Cancer Chemotherapy and Pharmacology (2019) 84:1333–1338
https://doi.org/10.1007/s00280-019-03968-2

ORIGINAL ARTICLE

Cisplatin ototoxicity in children: risk factors and its relationship with polymorphisms of DNA repair genes ERCC1, ERCC2, and XRCC1

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Received: 9 September 2019 / Accepted: 25 September 2019 / Published online: 4 October 2019

Abstract

Purpose We aimed to investigate the cisplatin-related hearing toxicity and its possible relationship with polymorphic variants in DNA repair genes, ERCC1, ERCC2, and XRCC1.

Methods Fifty patients treated with cisplatin in the past were included in the study. There were 29 females and 21 males; mean age 13.4 ± 6.0 years). The polymorphism in DNA repair genes was studied using primer and probes in Light Cycler device after DNA isolation was carried out with PCR technique. The polymorphisms and clinical risk factors were evaluated using Chi square test and logistic regression modelling.

Results The patients had hearing loss in 44%. For ERCC1 gene, the patients with hearing loss had 50% of GG (wild type), 40.9% of AG and 9.1% of AA genotypes, while the patients without hearing loss had 28.6% of GG, 53.5% of AG, and 17.9% of AA genotypes. For ERCC2 gene, the patients with hearing loss had 18.2% of GG (wild type), 40.9% of TG, and 40.9% of TT genotypes, while the patients without hearing loss had 10.7% of GG 39.3% of TG, and 50% of TT genotypes. For XRCC1 gene, the patients with hearing loss had 18.2% of CC (wild type), 59.1% of CT, and 22.7% of TT genotypes, while the patients without hearing loss had 35.7% of CC, 50% of CT, and 14.3% of TT genotypes. There was no statistically significant association among the groups ($p = 0.24$).

Conclusion We did not find a relationship between DNA repair gene polymorphisms and hearing toxicity of cisplatin.

Keywords Ototoxicity · Cisplatin · DNA repair genes · Polymorphism · Children

Introduction

Cisplatin and carboplatin are effective antineoplastic drugs for central nervous system tumors, osteogenic sarcoma, germ cell tumors, neuroblastoma, liver tumors and nasopharyngeal carcinomas in children. Platin drugs have many adverse effects such as nausea, vomiting, renal toxicity, ototoxicity and peripheral neurotoxicity. Renal and hearing toxicities are the dose-limiting major events in childhood cancer treatment. Carboplatin seems less toxic than cisplatin, however, its use is limited in some certain tumor types [1].

Hearing toxicity related with cisplatin is usually bilateral, irreversible and sensorineural in type in high frequencies [2–4]. The factors those affect ototoxicity are cumulative and repeating cisplatin doses, age less than 5 years, co-existence of renal disease, cranial irradiation and other autotoxic drugs such as aminoglycoside and furocemid [5–8]. Some adult and pediatric studies demonstrated that cisplatin ototoxicity might be related with DDIT4, NEK2, MYC genes, megalin, glutation S-transpherase, TPMT (Tiopurin-S-Metiltranspherase), COMT (Catechol-*O*-methyltransferase), ACYP2, GJB2, and SLC26A4 gene polymorphisms [9–14]. In a pharmacogenetic study including pediatric and adult patients with osteogenic sarcoma, polymorphic variants in DNA repair genes (ERCC2, XPC, XPA, ERCC1, ERCC4, and ERCC5) were found to be useful predictors for therapy response [3]. However, no study has been found so far

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focusing on polymorphic variants in DNA repair genes and their relationship with development of hearing toxicity in children.

In this study, we aimed to investigate cisplatin-related hearing loss in children, to analyze possible risk factors and their relationships with polymorphic variants in DNA repair genes, namely ERCC1 (rs25487), ERCC2 (rs13181), and XRCC1 (rs11615).

Patients and methods

Patients and setting

We have listed a total of 60 patients who are among long-term survivors or have completed their cisplatin treatment at least 6 months ago. These patients and families were reached by phone to invite to the study. Among them, fifty patients and families agreed to participate into the study. We, therefore, performed the analysis of prospectively collected data from 50 patients (29 female, 21 male) treated at the Pediatric Oncology Unit of Ege University Hospital, and 59 (29 female, 30 male) healthy controls. The study was approved by the local ethics committee, and informed consent was obtained from the parents or the patients who were above 18 years. The patient records were analysed in terms of demographic features, cumulative cisplatin doses, concomitant use of other ototoxic drugs, cranial irradiation, concurrent use of amifostin as a prevention for otoxicity and previous hearing test results. Exclusion criteria were a history of hearing impairment and traumatic brain injury before the cisplatin chemotherapy and having any disorders of external or middle ear.

All patients were treated by platin-based chemotherapy according to their cancer type. Eighteen patients (36%) were also treated with irradiation. During treatment regimens, audiometric analyses were performed on the patients by experienced technician at the audiometry laboratory before each cycle of cisplatin administrations.

At the beginning of this study, all patients were examined by an otolaryngologist for the external ear pathologies. Then, both patients and healthy controls were evaluated using pure tone audiometry, Distortion Product Otoacoustic Emissions (DPOAE) and Auditory Brainstem Response (ABR). Any hearing loss according to Brock staging, NCI staging or Chang staging was considered meaningful [15–17].

Materials

Peripheral blood samples were taken and stored at − 20 °C until use. Genomic DNA was extracted from peripheral blood leukocytes using the High Pure PCR Template Preparation Kit (Roche Applied Science, Mannheim, Germany) according to the manufacturer's protocol. For the analysis of the DNA repair genes polymorphisms following primer and probes (TIB MOLBIOL, Berlin, Germany) were used together with the LightCycler DNA Master Hybridization Probe Kit (Roche Diagnostics, Mannheim, Germany).

PCR protocol and genotyping

Real-time PCR experiments and melting curve analysis were performed using the LightCycler (2.0) instrument (Roche Applied Science, Mannheim, Germany) for the detection of the *ERCC1* (rs25487), *ERCC2* (rs13181) and *XRCC1* (rs11615) polymorphisms according to the Light Cycler DNA Master Hybridisation Probe Kit protocol. Polymorphic and wild-type alleles of the analysed genes were identified by the specific melting temperature (Tm) of the resulting products.

For the *ERCC1* (rs25487) gene polymorphism, individuals with two copies of the ancestral G allele (GG) showed a single melting peak at 71 °C and individuals with two copies of the polymorphic A allele (AA) also showed a single melting peak but at 66 °C, but individuals with both alleles (AG) showed two melting peaks at 66 °C and 71 °C in this analysis.

For the *ERCC2* (rs13181) gene polymorphism, individuals with two copies of the ancestral G allele (GG) showed a single melting peak at 73 °C and individuals with two copies of the polymorphic T allele (TT) also showed a single melting peak at 66 °C, but individuals with both alleles (GT) showed two melting peaks at 66 °C and 73 °C in this analysis.

For the *XRCC1* (rs11615) gene polymorphism, individuals with two copies of the ancestral C allele (CC) showed a single melting peak at 72 °C and individuals with two copies of the polymorphic T allele (TT) also showed a single melting peak but at 66 °C; but, individuals with both alleles (CT) showed two melting peaks at 66 °C and 72 °C in this analysis.

Statistical analysis

Statistical Package for the Social Sciences 22.0 package program (SPSS Inc; Chicago, IL, USA) was used for the analysis of data. Continual values of descriptive statistics were given as mean ± standard deviation (SD). Frequency analysis indicating incidence/frequence was stated in number and percentage (%). Chi square and Fischer exact tests were used to test the relationship between DNA repair gene polymorphisms and other risk factors. Also, logistic regression model was created using the risk factors that was found to be related with cisplatin ototoxicity in the univariate analyses. Statistical significance was accepted as p value less than 0.05.

Table 1 Treatment regimens for each cancer type

Cancer type	Treatment regimens
CNS tumors	POG 9031
Osteogenic sarcoma	EOI, Mayo Pilot II
Germ cell tumors	BEP
Neuroblastoma	TPOG Neuroblastoma 2003
Nasopharyngeal carcinoma	NPC-91-GPOH
Hepatoblastoma	SIOPEL

Table 2 Pathological diagnosis of the study group

The pathological diagnosis	*n*	%
CNS tumors	16	32.0
Medulloblastoma	9	
Pons glioma	2	
Anaplastic ependymoma	2	
Indifferentiated malign tumor	2	
Glioblastoma	1	
Osteogenic sarcoma	13	26.0
Germ cell tumor	7	14
Neuroblastoma	6	12.0
Hepatoblastoma	3	6.0
Nasopharynx carcinoma	3	6.0
Parotid mucoepidermoid carcinoma	2	4.0
Total	50	100.0

Results

The patient group consisted of 29 females and 21 males, whereas the control group consisted of 29 females and 30 males. Mean age was 13.9 ± 5.9 years in the patient group and 13.4 ± 3.7 years in the control group ($p = 0.59$). The pathological diagnoses are given in Table 1. CNS tumors and osteogenic sarcoma were the most common tumor types in the patient group.

Patients were treated according to the national or international protocols (Table 2). In the patient group, we found that 22/50 (44%) patients have hearing loss whereas the control group had normal hearing ($p = 0.000$). Among the patients with hearing loss, 6 had (27.3%) unilateral and 16 (72.7%) had bilateral loss. The patients with head and neck tumor (CNS tumors and nasopharyngeal carcinoma) (10/19) had similar hearing loss as compared to the non-head and neck tumor group (12/31) ($p = 0.39$).

Some demographic and clinical features of the patient group are given in Table 3. The mean cumulative cisplatin dose was 1275.7 ± 183.1 mg/m^2. Interestingly, hearing loss was found to be neither associated with cumulative cisplatin dose, nor age, head and neck irradiation, aminoglycoside use or amifostine use (Table 3). For the analysis purposes the patients were divided into two dose categories: (a) cisplatin less than 400 mg/m^2 (44 patients) and (b) cisplatin more than 400 mg/m^2 (6 patients). When we analysed the data in terms of cumulative cisplatin dose, both groups have similar incidence of hearing loss ($p = 0.23$) (Table 4). Of all patients, 13 (26%) patients had received amifostine during cisplatin treatment, among them 6 (27.3%) had developed hearing loss ($p = 0.33$) (Table 3).

Table 3 Demographic features and cumulative cisplatin dose of the study group according to hearing loss (mean ± SD)

	Hearing loss		*p*
	Yes	No	
Age	14.2 ± 6.3	13.6 ± 5.8	0.717
Diagnosis age	9.1 ± 5.2	9.6 ± 5.2	0.688
Cumulative cisplatin dose	319.8 ± 244.4	241.1 ± 107.6	0.363
Irradiation	9/18	9/18	0.522
Aminoglycoside use	4/13	9/13	0.263
Amifostin use	8/13	5/13	0.139

Table 4 The relationship between hearing loss and cumulative cisplatin dose

	Cumulative cisplatin dose		*p*
	< 400 mg/m^2	> 400 mg/m^2	
Hearing loss			
No	26	2	
Yes	18	4	0.233
Total	44	6	

ERCC1 (rs25487), ERCC2 (rs13181), and XRCC1 (rs11615) genes polymorphism were divided into three groups: wild type, heterozygous, and homozygous. The polymorphism analyses of the ERCC1, ERCC2, and XRCC1 genes of the patient and of the control groups are shown in Table 5. According to the Table 6, there was no statistically significant difference between three DNA repair gene polymorphisms (ERCC1, ERCC2, and XRCC1) and hearing loss ($p = 0.15$, $p = 0.62$, $p = 0.26$, respectively) (Table 5).

Discussion

One of the major events in cisplatin treatment is occurrence of ototoxicity [1]. This can occur during treatment and also many years after treatment. Cisplatin-induced ototoxicity is frequently bilateral, irreversible, and sensorineural in high frequencies. Speech and language development may be impaired as a result of hearing loss, and this may

Table 5 The mutation analyses of the ERCC1, ERCC2, and XRCC1 genes

	Patient [*n*, (%)]			Control [*n*, (%)]		
	Wild	Heterozygous mutant	Homozygous mutant	Wild	Heterozygous mutant	Homozygous mutant
ERCC1	19 (38)	24 (48)	7 (14)	29 (49.2)	25 (42.3)	5 (8.5)
ERCC2	7 (14)	20 (40)	23 (46)	10 (17)	26 (44)	23 (39)
XRCC1	14 (28)	27 (54)	9 (18)	18 (30.5)	32 (54.2)	9 (15.3)

Table 6 Comparison of DNA repair gene polymorphism (ERCC1, ERCC2, and XRCC1) and hearing loss

	Hearing loss [*n*, (%)]		Total	*p*
	Yes	No		
ERCC1				
Wild	11 (50)	8 (28.6)	19 (38)	0.15
Heterozygous	9 (40.9)	15 (53.5)	24 (48)	
Homozygous	2 (10)	5 (17.9)	7 (14)	
ERCC2				
Wild	4 (18.2)	3 (10.7)	7 (14)	0.62
Heterozygous	9 (40.9)	11 (39.3)	20 (40)	
Homozygous	9 (40.9)	14 (50)	23 (46)	
XRCC1				
Wild	4 (18.2)	10 (35.7)	14 (28)	0.26
Heterozygous	13 (59.1)	14 (50)	27 (54)	
Homozygous	5 (22.7)	4 (14.3)	9 (18)	
Total	22	28	50	

affect learning and school performance, psychosocial and emotional status and quality of life [1, 4, 5]. Kushner et al. reported that grade 3/4 hearing deficits affected 25% of the patients treated with cumulative cisplatin dose of 400 mg/m^2, 54% of the patients treated with 600 mg/m^2 and 50% of the patients treated with carboplatin-containing myeloablative therapy [5]. Post-chemotherapy ototoxicity was detected in 148 (48%) patients, and clinically significant ototoxicity was present in 91 (30%) in a large pediatric study carried out by Peleva et al. [3]. The authors reported similar ototoxicity in cisplatin and carboplatin administrations. In a large neuroblastoma series, Landlier et al. demonstrated that exposure to cisplatin combined with myeloablative carboplatin significantly increases hearing risk [6]. Patients treated with cisplatin alone (< 400 mg/m^2) or cisplatin (400 mg/m^2) plus carboplatin (1700 mg/m^2) had hearing loss according to Brock ranged from 8 to 30% [6].

It is clear that cisplatin, either alone or with carboplatin causes significant hearing loss. Those reported ototoxicity rates are high rate for an adverse effect that can affect children's life. In our patients who were treated with cisplatin only, hearing loss was documented in 22 out of 59 patients (44%), that is similar to the literature [3, 5, 6]. Cumulative cisplatin doses were similar in the patient group with or without hearing loss ($p = 0.67$ and $p = 0.59$, respectively). No significant association was found between hearing loss and other autotoxic drugs use.

As to carboplatin administration, hearing loss was reported in 20–25% in patients with retinoblastoma on carboplatin treatment [13, 18]. This hearing loss was strongly associated with age at diagnosis. Children, especially, received first dose of carboplatin before age of 4 months and had severe hearing loss. Yang et al. similarly found that hearing loss was related to younger age, and also craniospinal irradiation [7]. Children with CNS tumor treated with irradiation were also reported to have severe ototoxicity after treatment [1, 8]. In medulloblastoma patients, Paulino et al. figured out severe ototoxicity in 18.2% of ears in children treated with IMRT boost and cisplatin-based chemotherapy [8] Increasing dose to the cochlea was associated with increasing severity of hearing loss.

In our study population there were five patients who started to receive cisplatin before 6 months of age, and all had hearing loss at the time of this study. These patients did not receive any head-neck irradiation as part of their treatment. In the older group treated with cisplatin plus head and neck irradiation, the result did not differ in terms of hearing loss. This may be related with small sample size of our study.

Platin drugs exert their function by causing DNA cross-linking. Genes involved in drug transport, metabolism, and DNA repair regulate platinum toxicities [1]. Genetic factors and individual susceptibilities are also important in platin ototoxicity. Gene polymorphisms have been reported to have a role in the development of platin ototoxicity [11, 13, 19]. One of the early reports is associated with glutathione S-transferases (GSTs) and megalin. GSTs are isoenzymes involved in cellular detoxification processes, and megalin has been demonstrated to bind aminoglycosides, known to be similar to cisplatin for their ototoxicity [14]. GSTT1 wild genotype and C-allele of rs2228171 SNPs of megalin gene occurred with higher frequency in patients with ototoxicity as reported by Choeyprasert et al. [14].

Ross et al. identified genetic variants of TPMT and COMT associated with cisplatin-induced hearing loss in 54 children [19]. However, Yang JJ et al. demonstrated no

relationship between TPMT or COMT genetic variation and cisplatin ototoxicity in 213 children with medulloblastoma [7]. In 2014, a largest meta-analysis showed that the influence of TPMT and COMT on the development of cisplatin-induced hearing loss may be less important than previously suggested [20]. Similarly, in a series of retinoblastoma, no association was reported between genetic variants of TPMT, COMT and ABCC3 genes and hearing loss [13]. The association between TPMT, COMT, and ABCC3 variants and the hearing loss was also not observed in another cohort [21]. Thiesen et al. also did not find any relationship between TPMT and COMT polymorphisms and ototoxicity in 149 children; however, they found an association with ACYP2 polymorphism [22]. A recent 2019 meta-analysis including pediatric and adult data indicated that ACYP2, which plays a role in calcium homeostasis, increases the risk of ototoxicity LRP2 [2].

The role of WFS1 (wolframin ER transmembrane glycoprotein) in cisplatin-related ototoxicity was also investigated, and a statistically significant interaction between increasing cumulative cisplatin dose and rs62283056 genotype was found [11]. In a pediatric medullublastoma series, investigators found an association between hearing damage and rs4880 variant of SOD2 gene encoding manganese superoxide dismutase that increases hearing toxicity [12].

Excision repair cross-complementation group 1 (ERCC1) is the lead enzyme in the nucleotide excision repair process [23]. Polymorphisms of the genes involved in cisplatin–DNA adduct repair (ERCC1, ERCC2) can increase the risk of cisplatin-associated toxicity [1, 24]. Carrying at least one variant ERCC1 C8092A allele was associated with a significantly increased risk of grade 3 or 4 gastrointestinal toxicity in adults with lung carcinoma [24]. There are limited number of studies with ERCC1 and ERCC2 gene polymorphisms in children, but no study was found with XRCC1 gene polymorphism. Caronia et al. investigated whether eight single-nucleotide polymorphisms in ERCC2, XPC, XPA, ERCC1, ERCC4 and ERCC5 genes were associated with tumor response and survival in osteosarcoma patients treated with cisplatin [9]. They found a significant association with tumor response for the Lys751Gln polymorphism in the ERCC2 gene. But they found weak evidence of an association with the CC genotype of XPC. Obiedat et al. also found that a positive and significant association between ERCC1 C8092 A genotypes and less event-free survival rate. But, they did not report any susceptibility to hearing loss in the study [25].

The XRCC1 gene is a member of the base excision repair pathway, a much more specific pathway that consists of multiple enzyme systems, each of which is specific for a particular type of base damage [26]. In NSCLC patients, the A/A or G/A genotypes have been associated with increased risk of all toxicities as compared with the G/G genotype, and particularly with a 2.5-fold increased risk of grade 3 or 4 gastrointestinal toxicities [26]. The XRCC1 gene was not studied to date in terms of hearing toxicity of cisplatin.

In contrast to the literature findings, we did not show any significant association between the ERCC1, ERCC2, and XRCC1 gene polymorphisms and ototoxicity of cisplatin in our study.

As a result, we conclude that our findings in this pharmacogenetic study do not support any relationship between cisplatin ototoxicity and DNA repair gene polymorphisms, ERCC1 (rs25487), ERCC2 (rs13181), and XRCC1 (rs11615), in children. Possible relationship between DNA repair genes and susceptibility to cisplatin ototoxicity should be searched in large future studies. Even though, we might have found cumulative cisplatin dose was not related with ototoxicity, this might be due to the small sample size of this study. Nevertheless, cisplatin ototoxicity remains an important health problem in the long-term survivors of childhood cancer.

Compliance with ethical standards

Conflict of interest The author(s) declare that they have no competing interests.

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