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Ototoxicity in Cisplatin-treated nasopharyngeal carcinoma in children

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Abstract

Introduction: The most prevalent malignancy, Nasopharyngeal Carcinoma (NPC), occurs at the nasopharynx, affecting men more than women. The standard gold method for the management of patients with NPC is a combination of radiotherapy (RT) and chemotherapy. The most ototoxic and widely used platinum-based chemotherapy in the management of patients with NPC is cisplatin.

Aim of the study: To determine the incidence of ototoxicity after chemoradiotherapy in children suffering from nasopharyngeal carcinoma.

Subjects and Methods: We enrolled 68 children suffering from nasopharyngeal carcinoma and treated them with chemotherapy or chemoradiotherapy in the time period from 2011 to 2019—50 males and 18 females. We conducted audiometry and tympanometry to assess the hearing system before the start of therapy and after each cycle of treatment with cisplatin.

Results: Before, during, and after the chemotherapy cycle, audiometry of the included patients revealed that 33 patients had no hearing loss. The rest were diagnosed with hearing loss (21 patients with SNHL, 9 patients with CHL, and five patients with mixed hearing loss). Hearing evaluation in the right ear showed that 35 patients had no hearing loss, 21 patients had SNHL, 5 patients had CHL, and five patients had mixed hearing loss. Hearing thresholds in the left ear revealed normal hearing in 36 patients, while 22 patients had SNHL, 4 patients had CHL, and four patients had mixed hearing loss.

Conclusion: Treatment of NPC with RT and concurrent cisplatin has been shown to cause a significant ototoxic effect, especially with long-term administration of chemoradiotherapy, and the physician should be aware of the possible hearing impairment. The patients should be carefully monitored to prevent the progression and permanent damage to the hearing system

Keywords: nasopharyngeal carcinoma; cisplatin; radiotherapy; ototoxicity.

1. Introduction

Squamous cell carcinomas are the most common tumors to develop in the head and neck. The pharyngeal recess, or fossa of Rosenmuller, is the most typical location of origin [1, 2]. Oncogenesis caused by viruses frequently occurs in head and neck tumors [3]. The precise etiology is still a mystery. However, EBNA1, LMP-1, and LMP-2 viral

oncogenes are recognized to have a significant impact [4].

Based on histology, the World Health Organization (WHO) divided nasopharyngeal carcinoma into three subgroups [5]. Type 1 keratinizing squamous cell carcinoma is linked to EBV infection in 70% to 80% of patients. Type 2 nasopharyngeal cancer is differentiated non-keratinizing carcinoma, and type 3 is undifferentiated non-keratinizing carcinoma. The latter two categories are also the most sensitive to therapy [6].

Radiotherapy is the mainstay of NPC treatment, with chemotherapy added in cases of severe disease [7]. Chemoradiotherapy is the cornerstone of management in locally progressing regional illness, whether through induction or concurrent therapy methods. Cisplatin is the initial agent to be utilized. The recommended dosage is 100 mg every third week. Palliative chemotherapy is offered to NPCs with distant poly-metastases [8]. 5-fluorouracil and cisplatin are the preferred drugs. Several chemotherapeutic drugs are now available for the course of therapy, thanks to recent advancements [9, 10].

Cisplatin is linked to irreversible ototoxicity, which affects up to 25% of adult patients, despite being quite effective for NPC [11]. A pattern of bilateral high-frequency hearing loss that might appear days to weeks following therapy characterizes this condition. Cumulative cisplatin dose, cranial irradiation, and young age are risk factors for cisplatin-induced ototoxicity. It is essential to have a clear picture of how severe cisplatin-induced ototoxicity is in patients with NPC to decide on the right monitoring and preventative measures [12]. As a result, it's essential to understand how to discriminate cisplatin-caused ototoxicity from RT effects in these people [13].

In the current study, we aimed to determine the incidence of ototoxicity after chemotherapy and radiotherapy in children suffering from nasopharyngeal carcinoma.

2. Subjects and methods

2.1. Subjects

We periodically tested the patient's hearing before and after chemoradiotherapy. Children with NPC who visited the head and neck clinic between 2011 and 2019 were identified using a retrospective examination. As part of their usual care, patients with NPC undergo pretreatment and posttreatment audiometry due to the potential synergistic effects of RT and cisplatin on hearing.

In the current retrospective study, we enrolled 68 children complaining of nasopharyngeal carcinoma and treated them with chemotherapy and chemoradiotherapy in the time period from 2011 to 2019.

Inclusion criteria

Any patient with a histologically confirmed diagnosis of primary NPC, treated with chemoradiotherapy, or suffering from non-metastatic NPC was included.

Exclusion criteria

Patients underwent surgical management, treated with radiotherapy only, or suffering from metastatic NPC were excluded.

Ethical consideration

The Faculty of Medicine Research Ethical Committee evaluated this study. The researchers explained to the participants the goals of the study, the test, and the upcoming investigation. Additionally, they must respect the privacy of personal data and their freedom to decline to take part in the study. All participants in the study provided written informed consent.

2.2. Methods

Medical History

Full history was taken from the included patients, such as demographic data (gender, age), general medical history (previous surgeries, previous medications), and audiological history (hearing loss, ear pain, tinnitus).

Outcomes

Audiometry was done before the management, after each cycle of HD Cisplatin, before Rth/Cisplatin, after Rth/Cisplatin, and every six months in the follow-up period.

Methods of Audiologic Monitoring

Baseline testing should be obtained before the start of chemotherapeutic agents, especially cisplatin and carboplatin. Patient selection, complicating medical factors, level of consciousness, and age play a role in selection methods for early detection. Bilateral PTA air conduction thresholds at standard audiometric frequencies from 0.25 to 8 kHz should be obtained. Additional testing would include a case history including family history, otoscopic examination, immittance or bone conduction testing, speech reception threshold, and word recognition scores. For any sign of ototoxicity, the auditory measure should be done for early detection of ototoxicity. For chemotherapeutic medications, weekly testing is recommended, and the interval for testing should decrease with the early signs of ototoxic change. Monitoring should continue for at least 3-6 months following the cessation of the potentially ototoxic medications or with the hearing stabilization.

2.3. Statistical Analysis

These data were analyzed using SPSS (Statistical Package for Social Sciences) for the windows release 10.0 program. Descriptive and Analytic statistics were conducted using mean and standard deviation and frequencies as numbers and percentages.

3. Results

The current study recruited 68 patients. The mean age of the included participants was 13.5 ± 2.6 and distributed as 50 males and 18 females. Three cases died during the study period, and 53 patients completed the study (Table 1).

Table 1: The baseline characteristics of the included participants.

Variables		Frequency (%)
Gender	Male	39 (70.9%)
	Female	16 (29.1%)
Death Status	Dead	3 (5.5%)
	Alive	52 (94.5%)

Before starting the treatment in the right ear, 35 patients did not have hearing loss; 21 patients have sensorineural hearing loss (SNHL). Regarding the left ear, 36 cases did not have hearing loss (Table 2).

Table 2: Etiology of AKI and CKD in the study population.

Variables		Frequency (%)
Type of AM in the right ear before treatment	No	32 (58.2%)
	SNHL	6 (10.9%)
	CHL	10 (18.2%)
	Mixed	3 (5.5%)
Type of AM in the left ear before treatment	No	37 (67.3%)
	SNHL	4 (7.3%)
	CHL	10 (18.2%)
	Mixed	1 (1.8%)

Pre, during, and post-chemotherapy audiometry of the included patients revealed that 35 patients had not had any hearing loss, while the rest had been diagnosed with hearing loss (21 patients with SNHL, 5 patients with CHL, and five patients with mixed hearing loss). In the left ear, 36 patients had no hearing loss, 22 patients had SNHL, four patients had CHL, and four patients had mixed hearing loss. Regarding the degree of hearing loss in the right ear, two patients had mild hearing loss, 17 patients suffered from moderate hearing loss, four patients had mild to moderate hearing loss, two patients had mild to moderately severe hearing loss, three patients had moderately severe hearing loss, one had mild to severe hearing loss, one had moderate to severe hearing loss, and one had severe hearing loss. In the left ear, 35 patients had no hearing loss, seven patients had mild hearing loss, four patients had mild to moderate hearing loss, two patients had mild to moderately severe hearing loss, 11 patients had moderate hearing loss, one patient had mild to severe hearing loss, two patients had moderate to moderately severe hearing loss, one patient had moderate to severe hearing loss, and two patients had moderately severe hearing loss (Table 3).

Table 3: The types and degrees of audiometry in each ear.

Variables		Frequency (%)
Type of AM in the right ear	No	29 (52.7%)
	SNHL	14 (25.5%)
	CHL	6 (10.9%)
	Mixed	3 (5.5%)
	Total	52 (94.5%)
Type of AM in the left ear	No	30 (54.5%)
	SNHL	13 (23.6%)
	CHL	6 (10.9%)
	Mixed	3 (5.5%)
	Total	52 (94.5%)
Degree of AM in the right ear	No	29 (52.7%)
	Mild	2 (3.6%)
	Moderate	15 (27.3%)
	mild to moderate	2 (3.6%)
	mild to severe	1 (1.8%)
	Moderate to severe	3 (5.5%)
	Total	52 (94.5%)
Degree of AM in the left ear	No	30 (54.5%)
	Mild	10 (18.2%)
	Moderate	7 (12.7%)
	Mild to moderate	3 (5.5%)
	mild to severe	1 (1.8%)
	moderate to severe	1 (1.8%)
	Total	52 (94.5%)

Forty-nine cases had normal ear pressure, while 19 cases had abnormal ear pressure. In the right ear, nine cases had otitis media, and one case had Eustachian tube dysfunction. In the left ear, seven cases had otitis media and two cases had eustachian dysfunction (Table 4).

Table 4: The ear pressure after five cycles of treatment.

Tympanogram (ear pressure)	Normal Tympanogram	Otitis media on Tympanogram
Right ear	40 (72.7%)	42 (76.4%)
Left ear	11 (20%)	9 (16.4%)

4. Discussion

NPC is the most prevalent malignancy occurring at the nasopharynx, affecting males more than females [14]. The gold standard method for the management of patients with NPC is a combination of RT and chemotherapy, especially for those with advanced stages of the disease [15]. Platinum-based drugs are common curative and palliative chemotherapies utilized for a variety of cancers affecting both adult and pediatric populations, including NPC. One of the most important adverse effects of platinum-based agents is ototoxicity and hearing loss. It is a hearing disorder that results from either temporary or permanent ear dysfunction [16].

In this retrospective study, we aimed to determine the incidence of ototoxicity after chemo-radiotherapy in children suffering from NPC. We analyzed 68 children with NPC who received five cycles of cisplatin as a chemotherapeutic agent in addition to RT. All patients were assessed by audiometry before and after the start of chemotherapy due to the potential synergistic effects of RT and cisplatin on hearing. Post-treatment audiometry in the right ear revealed that 30.8%, 7.3%, and 7.3% of children developed SNHL, CHL, and mixed hearing loss, respectively. On the other hand, the left ear audiometry showed that 32.3%, 5.8%, and 5.8% of children developed SNHL, CHL, and mixed hearing loss, respectively, which are comparable results to the right ear. Of those children, two patients in the right ear and seven in the left ear suffered from mild hearing loss, while 17 patients in the right ear and 11 patients in the left ear suffered from moderate hearing loss, four patients suffered from mild to moderate hearing loss in the right and left ears, two patients suffered from mild to moderately severe hearing loss in the right and left ears, three patients suffered from moderately severe hearing loss, and one patient suffered from severe hearing loss in the right ear, respectively. One patient suffered from mild to severe hearing loss, two patients suffered from moderate to moderately severe hearing loss,one patient suffered from moderate to severe hearing loss, and one patient suffered from severe hearing loss in the left ear, respectively.

Cisplatin is the most ototoxic drug that may cause bilateral tinnitus and high- and low-frequency SNHL with a 20–84% incidence rate on long-term administration of the drug [17–20], which is similar to our analysis, which showed that approximately 25% of our patients developed SNHL. The production of free radicals, which may

destruct the cochlear hair cells, spiral ganglion cells, supporting cells, and marginal cells of the stria vascularis, is the primary cause of the cisplatin ototoxic effect [20–21]. Previous studies showed a significant association between the extent of hearing loss and both the dose and duration of concurrent cisplatin and RT; the history of the method of administration may play a role in determining the degree of hearing loss [22–24]. A previous phase III randomized trial of patients with stage III and IV NPC was conducted [25]. Investigating the overall survival and progressive-free survival (PFS) of patients who received either RT alone or combined RT and concurrent cisplatin followed by adjuvant chemotherapy with cisplatin and fluorouracil infusion, the overall survival and PFS were significantly better in the combined group, which was the conclusion. Other studies demonstrated that after the treatment of NPC, about 30% of patients develop significant SNHL, which is consistent with our findings [26–28]. To date, the US Food and Drug Administration (FDA) has not approved any otoprotective agent that can be routinely used to prevent cisplatin-induced ototoxicity or vestibulo-toxicity [29–30]. However, rehabilitation programs and advanced hearing aids had been developed to improve hearing disabilities, not to restore the damaged system [31]. A previous retrospective study evaluated the association between the implications of cisplatin dose and cochlear/inner ear radiation dose and their impact on early and late hearing impairment. They found that cisplatin alone and radiation alone could have an independent negative effect on patients. Dose-dependent ototoxicity from cochlear radiation was not increased by the induction and concurrent doses of cisplatin [32]. A previous trial reported that the overall toxicity of concurrent chemo-radiotherapy was significantly higher than the toxic effect of RT alone [33]. Neurotoxicity, nephrotoxicity, or cardiotoxicity might occur in addition to the ototoxic effect of cisplatin. Therefore, its utilization is decreasing over time, and there are great efforts to use alternative new combined chemotherapeutic drugs with higher efficacy and a better safety profile [34].

Our study had some limitations, such as its retrospective nature, the relatively small sample size, and the fact that some patients were lost in the follow-up period. Moreover, we could not assess the independent effect of RT and cisplatin on the patient's hearing system.

Conclusion

To conclude, treatment of NPC with RT and concurrent cisplatin has been shown to cause a significant ototoxic effect, especially with long-term administration of the chemo-radiotherapy. A physician should be aware of the possible hearing impairment effect, and the patients should be carefully monitored to prevent the progression of permanent damage to the hearing system. Further high-quality, evidence-based studies with a large sample size are needed to establish the association between chemo-radiotherapy and hearing impairment.

Ethical Approval Statement: The Faculty of Medicine Research Ethical Committee evaluated this study. The researchers explained to the participants the goals of the study, the test, and the upcoming investigation. Additionally, they must respect the privacy of personal data and their freedom to decline to take part in the study. All participants in the study provided written informed consent.

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Conflicts of Interest: All authors declare no conflict of interest.

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