



Ototoxicity after chemoradiotherapy for nasopharyngeal carcinoma

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Abstract: Successful nasopharyngeal carcinoma (NPC) treatment increases the survival rate and increases the late toxicity of chemoradiotherapy in survivors. Ototoxicity is the most common severe late sequelae after treatment. Both cochlear toxicity and vestibular toxicity have a significant negative impact on the quality of life. The hearing loss may begin as early as after the completion of radiotherapy (RT). Determination of rate of hearing loss after treatment completion is varied, depending on many factors, such as ototoxicity grading scales, follow-up period, treatment modalities, RT techniques. Prevalence of vestibular toxicity and tinnitus are also varied, depending on subjective or objective findings, types of vestibular function tests, or questionnaire. Successful ototoxicity monitoring involves the effort of healthcare professional teamwork. Permanent damage to the hearing and balance system can be decreased by early identification and promptly appropriate actions. Currently, there is no otoprotective agent recommended routinely to prevent ototoxicity after chemotherapy or radiation therapy. Rehabilitation options may improve the symptom disability but not restore the damage. The patient care team should be aware of the early identification of the ototoxicity. Effective tools for monitoring reveal abnormalities before the presence of audiovestibular symptoms. Once the ototoxicity was detected, the patient care team should consider starting appropriate actions to prevent progression and permanent damage. This article presents factors associated with an increased risk of hearing loss after treatment, ototoxicity grading scales, and tools of ototoxicity monitoring.

Keywords: Ototoxicity; cochlear toxicity; vestibular toxicity; nasopharyngeal carcinoma (NPC); chemoradiotherapy; hearing loss

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Introduction

Ototoxicity is defined as damage to the inner ear structures (cochlea and vestibule) and functions after exposure to medication or other substances (1,2). With the improvement of the treatment of nasopharyngeal carcinoma (NPC), the overall survival rate has increased as well as the incidence of late toxicities. Ototoxicity is the most common severe late toxicity in NPC survivors, 71% of overall cases (3). Although not itself fatal, hearing impairment, imbalance, and tinnitus

showed significant negative impacts on psychological status and quality of life. Half of the patients who received cisplatin developed permanent SNHL (4). Hearing loss decreases the health-related quality of life (5) and increases depressive and anxiety symptoms as well as dementia (5-7). In children, hearing loss results in learning problems by influencing speech and language development (8).

Determination of rate of hearing loss after treatment completion is varied, depending on many factors, such as

ototoxicity grading scales, follow-up period, treatment modalities, radiotherapy (RT) techniques. Most of the NPC cases received combined chemotherapy and RT. There are limited data on the incidence of hearing loss after NPC treatment with chemotherapy alone or RT alone. Compared to other cancers, hearing loss after NPC treatment is not only sensorineural hearing loss (SNHL) resulted from the ototoxic effect of the treatment, but also conductive hearing loss resulted from external and middle ear pathology.

The platinum compounds, such as cisplatin, carboplatin, and oxaliplatin are highly effective against a variety of malignancies (9). The most commonly used systemic drug for head and neck squamous cell carcinoma is cisplatin. The ototoxins cross the blood-labyrinth barrier and enter the cochlea. The ototoxic drugs induce damage to the sensory hair cells, nonsensory cells, and the neural pathway to the cortex (1). SNHL from platinum-induced ototoxicity is bilateral, progressive, and irreversible (9). Incidence of cisplatin-induced ototoxicity after treatment for various types of cancers was 37–94% in children and 33–92% in adults (10). In head and neck cancer patients, high cisplatin dose, e.g., 100 mg/m² every three weeks resulted in a higher rate of hearing loss than low cisplatin dose, e.g., 40 mg/m² weekly (11).

The incidence of hearing loss of platinum-compound seems to depend on the type of platinum-compound used cumulative doses, individual doses, infusion durations (12). Carboplatin and oxaliplatin cause less hearing loss than cisplatin (13). The high-frequency hearing threshold of NPC patients after treatment by RT combined with cisplatin was higher than treatment by RT combined with carboplatin and by radiation alone (14). Rate of delayed latency of wave V of the auditory brainstem response (ABR) and abnormal audiograms in cancer patients who received cisplatin was higher than in those who received carboplatin (15).

Radiation can damage the sensory hair cell, microcirculation in the cochlea, and impair the retrocochlear auditory pathway then induce hearing loss (16). The greater total radiation dose, the greater incidence of the hearing loss, especially if the nasopharynx dose was >72 Gy (17), or the cochlea dose was >50 Gy (18). RT alone with doses of <40 Gy did not show hearing loss (11). SNHL induced by RT is progressive (17). The incidence and severity of hearing loss after RT increased over time (16). The RT-induced SNHL usually presents clinically at least 12 months after completing RT (17,19). However, the SNHL may begin as early as after the completion of RT (20). An increased hearing threshold was observed only in high frequencies at

one-month post-radiation. The hearing threshold of speech frequencies was later increased, at 12, 24, and 60 months post-radiation (16). Incidence of hearing loss after treatment for NPC with RT was 37–85.5% (16,20–22), with intensity-modulated radiation therapy (IMRT) was 37% to 51.2% at high frequencies and 6% to 22% at low frequencies (23). Cochlear radiation at doses above and below 60.5 Gy showed significantly increased 5-year and 10-year actuarial risk of clinically overt SNHL at 37% and 3% (24).

Synergistic ototoxicity in combined cisplatin and radiation therapy has been *in vitro* confirmed, increased apoptotic cell deaths (25). Clinically, in NPC patients after completion of chemoradiotherapy, the hearing threshold was higher than those who received RT alone (17,26). A radiation dose >72 Gy and conformal RT resulted in more severe hearing loss than <72 Gy and IMRT (17). Incidence of hearing loss after treatment NPC (I) with conventional or conformal radiation therapy and chemotherapy was 5–82% (18,27–29). One report found 93.8% had bilateral hearing loss in which 57.3% had a moderately severe loss or worse (14). (II) With IMRT and chemotherapy was 37–42% at 4 kHz and 7–13% at 0.5–2 kHz (18,23). After concurrent and induction chemoradiotherapy for NPC with cisplatin, hearing threshold, compared to baseline, at 4 and 8 kHz was increased at one and three months and plateaued about 3 and 6 months (30).

Compared to the rate of hearing loss, fewer numbers of studies reported the rate of vestibular toxicity and tinnitus after chemotherapy and RT. Prevalence of vestibular toxicity and tinnitus are varied, depending on subjective or objective findings, types of vestibular function tests, or questionnaire. The prevalence seems to be under-investigated and underestimated (6,31).

After chemotherapy, the rate of abnormal vestibular function tests detected by the caloric test was 0–50%, by the rotational test was 0–31%, by the horizontal video head impulse test (vHIT) was 25%. The rate of vestibular symptoms was 0–42%. Asymptomatic patients may show abnormal vestibular function tests. To detect vestibular toxicity, clinicians cannot rely on symptoms only (31). The rate of tinnitus after platinum-based chemotherapy and/or RT was 10–67%. Some patients who complained of tinnitus reported no hearing symptoms and showed normal hearing tests (6). Data on radiation effects on vestibular function and tinnitus are limited.

Currently, there are no FDA-approved drugs (32) and no otoprotective agent recommended routinely to prevent cisplatin ototoxicity (10). Also, no approved preventive

Table 1 Factors associated with an increased risk of hearing loss after chemoradiotherapy

Factors	Factor characteristics
Cochlear dose	>40 Gy (6), ≥45 Gy (34), >47 Gy (22), >48 Gy (35), ≥50 Gy (36), >50 Gy (18,37), ≥55 Gy (19), ≥60 Gy (38)
Inner ear dose	>45 Gy (18)
Internal acoustic canal dose	>50 Gy (18)
Nasopharynx dose	>72 Gy (12,39)
Radiation techniques	2D-3D CRT (worse than IMRT) (12)
Cisplatin	Cumulative dose 200 mg/m ² (18,36) 3-week high-dose regimen (worse than non-high-dose regimen) (3)
Treatment regimen	Chemoradiotherapy (worse than RT alone) (12,21)
Patient characteristic	Male (worse than female) (24) Baseline hearing threshold <60 dB at 4 kHz (40) Age >50 years (19,40) Presence of otitis media with effusion (19)

modality exists for vestibulotoxicity after chemotherapy and for cochleotoxicity or vestibulotoxicity after radiation therapy. Modern hearing devices and advanced rehabilitation options improve the hearing ability but not restore the damage (33). The patient care team should be aware of the early identification of the ototoxicity.

This article highlights the clinical approach and monitoring of ototoxicity after chemoradiotherapy for NPC. The information regarding mechanism and pathophysiology (4-6), updating on the otoprotective agent (12), and other interesting scopes of ototoxicity are available in other resources.

Ototoxicity risk factors

Evidence-based supported factors that influenced the risk of ototoxicity after chemoradiotherapy for NPC mainly focused on SNHL and the use of cisplatin. The factors associated with a significant increase in the risk of hearing loss are shown in *Table 1*. Systematic review studies reported the risk factors of SNHL after RT and/or chemotherapy for head and neck cancer have been published (19,41), but not an NPC.

Ototoxicity grading scales

Grading scales of ototoxicity were developed for early detection and monitoring of the cochlear and vestibular dysfunction. These scales have been used to report the

deterioration of hearing threshold, the severity of hearing impairment, and the severity of vestibular dysfunction (8,42,43). Most of the scales, again, more emphasized on cochleotoxicity than on vestibulotoxicity. Crundwell *et al.* [2016] reviewed 13 key classification systems for cochleotoxicity monitoring which focus on hearing change from a baseline audiogram or focus on the functional impact of the hearing loss (43). The most widely used scales are the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) scale, Brock's scale, and the ASHA scale (43-45).

The variation of the grading scales results in the difference of ototoxicity incidence which depends on how hearing loss is defined. Scales for report the cochlea dysfunction are shown in *Table 2*. Scales for reporting the vestibular loss and tinnitus are shown in *Table 3*.

Ototoxicity monitoring

Developing of an ototoxic monitoring program required these professional collaborations. However, surveys conducted in the United States and the United Kingdom, where national audiology guidelines for monitoring patients receiving ototoxic drug treatments are available, have shown that less than half of the respondents have an audiology ototoxic monitoring program (28,44).

Successful of ototoxicity monitoring in NPC patients treated with chemoradiation involves the effort of healthcare

Table 2 Ototoxicity grading scales for detection hearing impairment

Grading system	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
CTCAE v5.0 2017, (46)	–	Threshold shift of 1, 2, 3, 4, 6, and 8 kHz, at least one ear			The absolute threshold at 2 kHz and above
		Pediatric			
		>20 dB, at >4 kHz	>20 dB at 4 kHz	>20 dB at 2 to <4 kHz	>40 dB HLSNHL; audiologic indication for cochlear implant
		Adults enrolled in a Monitoring Program			
		15–25 dB, averaged at 2 contiguous test frequencies	>25 dB, averaged at 2 contiguous test frequencies	>25 dB, averaged at 3 contiguous test frequencies	>80 dB HL; non-serviceable hearing
		Adults not enrolled in a Monitoring Program			
		Subjective change in hearing in the absence of documented hearing loss	Hearing loss with hearing aid or intervention not indicated. Limiting instrumental ADL	Hearing loss with a hearing aid or intervention indicated. Limiting self-care ADL	–
TUNE 2014, (47)	No hearing loss	Threshold shift (AC-pure tone average)		Hearing level (AC-pure tone average)	
		1a ≥ 10 dB at 8–10–12.5 kHz; 1b ≥ 10 dB at 1–2–4 kHz	2a ≥ 20 dB at 8–10–12.5 kHz; 2b ≥ 20 dB at 1–2–4 kHz	≥ 35 dB at 1–2–4 kHz	≥ 70 dB at 1–2–4 kHz
SIOP 2012, (32)	Sensorineural hearing thresholds (dBHL) AC or BC with a normal tympanogram				
	≤ 20 dB HL all frequencies	>20 dB HL SNHL, at >4 kHz	>20 dB HL SNHL, at ≥ 4 kHz	>20 dB HL SNHL at ≥ 2 or 3 kHz	>40 dB HL SNHL at ≥ 2 kHz
Chang 2010, (48)	Sensorineural hearing threshold (dB HL) AC or BC with a normal tympanogram				
	≤ 20 dB at 1, 2, and 4 kHz	1a ≥ 40 dB at any frequency 6–12 kHz; 1b >20–<40 dB at 4 kHz	2a ≥ 40 dB at ≥ 4 kHz; 2b >20–<40 dB at any frequency <4 kHz	≥ 40 dB at >2 or 3 kHz	≥ 40 dB at ≥ 1 kHz
Muenster 2007, (49)	Normal ≤ 10 dB HL all frequencies	Beginning hearing loss >10–20 dB at least one frequency or tinnitus	Moderate impairment at ≥ 4 kHz; 2a >20– ≤ 40 dB; 2b >40– ≤ 60 dB; 2c >60 dB	Severe impairment, hearing aids needed at <4 kHz; 3a >20– ≤ 40 dB; 3b >40– ≤ 60 dB; 3c >60 dB	Loss of function, CI indication, average hearing loss at <4 kHz ≥ 80 dB
POG 1999, (9)	Normal: no change	Mild 20–40 dB loss at >4 kHz	Moderate >40 dB loss at >4 kHz	Severe >40 dB loss at >2 kHz	Unacceptable 40 dB loss at <2 kHz
ASHA 1994, (45,50)	(a) ≥ 20 dB decrease at any one test frequency, (b) ≥ 10 dB decrease at any two adjacent frequencies, or (c) loss of response at three consecutive frequencies where responses were previously obtained. Changes are always computed relative to baseline measures				
Brock 1991, (51)	Absolute threshold				
	<40 dB all frequencies	≥ 40 dB at 8 kHz	≥ 40 dB at ≥ 4 kHz	≥ 40 dB at ≥ 2 kHz	≥ 40 dB at ≥ 1 kHz

Table 2 (continued)

Table 2 (continued)

Grading system	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
WHO 1991, (52,53)	Better ear				
	No impairment <25 dBHL	Slight impairment 26–40 dBHL	Moderate impairment 41–60 dBHL	Severe impairment 61–80 dBHL	Profound impairment ≥81 dBHL

CTCAE v5.0 = Common Terminology Criteria for Adverse Events version 5.0; U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute; for chemotherapy-induced hearing loss; *The TUNE grading system*; high-frequency audiometry (HFA) in an adult; *The SIOP* (International Society of Pediatric Oncology) Boston ototoxicity scale; for platinum-induced ototoxicity in Children at the end of treatment of a clinical trial; *Brock grading system*; for children with a malignant tumor treated with cisplatin; *Chang grading system*; modification of the Brock scale; for oncologic children treated with cisplatin and carboplatin; *Muenster classification high frequency* for hearing loss following cisplatin chemotherapy; POG, Pediatric Oncology Group criteria; for children treated with chemotherapy; ASHA, American Speech-Language-Hearing Association, Changes must be confirmed by repeat testing, generally within 24 hours; *The Brock grading system*; for pediatric patients treated with cisplatin; WHO, World Health Organization; AC, air-conduction; BC, bone-conduction.

Table 3 Ototoxicity grading scales for detection vestibular dysfunction and tinnitus

CTCAE v5.0 2017, (46)	Grade 1	Grade 2	Grade 3
Tinnitus	Mild symptoms: intervention not indicated	Moderate symptoms: limiting instrumental ADL	Severe symptoms: limiting self-care ADL
Vertigo	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self-care ADL
Vestibular disorder	–	Symptomatic; limiting instrumental ADL	Severe symptoms; limiting self-care ADL

ADL, activities of daily living.

professional teamwork which include (I) audiological professionals (e.g., audiologists, audiovestibular physicians, otolaryngologist, neurotologist and (II) oncology professionals e.g., head and neck oncologist, radiation oncologist, medical oncologist, specialist nurses, pharmacists, and also positive patient-clinician relationships (2,28,54,55). Once chemotherapy or RT has been started, the patient should be scheduled for ototoxicity monitoring before each treatment session if possible. However, the patients may be too ill or unable to complete the tests. Modification of the monitoring protocol must be considered (2).

Ototoxicity monitoring protocols mostly referred to cochleotoxicity from platinum-based chemotherapy in terms of hearing loss. Audiologic ototoxic monitoring program (AOMP) aims for early identification and early intervention (45). Three phases of an AOMP consist of (I) baseline (pretreatment), (II) serial (during treatment), and (III) maintenance (posttreatment) (2,45).

In baseline evaluation, clinicians should (I) review causes of hearing loss (e.g., family history, noise exposure, previous ototoxic use, or ear disease, etc.); (II) review potentiate

risk factors for ototoxicity, e.g., poor renal function, use of other ototoxic agents, and previous noise exposure; (III) otoscopy (2,28). About one-third of NPC patients had otitis media with effusion (OME) at the time of diagnosis (56) and suffered from IMRT-induced chronic suppurative otitis media or post-irradiation OME (57,58). Normal tympanic membrane defines as translucent, gray color, with a cone of light reflex, fully mobile under pneumatic otoscopy. OME should be diagnosed if retracted tympanic membrane, opaque, amber color, decreased mobility, or visible of air-fluid level or air-bubbles behind it (59,60). Tympanometry should be used to confirm the presence of the OME especially in an ear with uncertain otoscopic findings. For interpretation of type B tympanogram, equivalent ear canal volume, which estimates the amount of air in front of the probe, must be in the normal range (60) (05–1 mL in children; 0.6–2.0 mL in adults) (61).

Ideally, baseline audiometric tests should be performed before starting the first treatment. If not possible, 1 week prior to or within 24 hours after the first treatment using either cisplatin or carboplatin is acceptable (2,45).

Three main baseline audiological tests in the past decades included (I) pure-tone audiometry (PTA; 0.25–8 kHz), (II) high-frequency audiometry (HFA; 9–20 kHz), and (III) distortion product otoacoustic emission (DPOAE) (50). At present, more testing needed (I) to determine effects of other factors such as speech audiometry [including speech reception threshold (SRT) and word recognition or speech discrimination score] (2,45), speech audiometry in quiet and in noise (6), (II) to increase sensitivity for detection of the cochlear damage such as a limited behavioral test frequency range [sensitive range of ototoxicity using PTA and HFA; SRO_{BEH} (62) and sensitive range of ototoxicity using DPOAE; SRO_{DP} (55)]. ABR, an objective test for evaluating changing of hearing threshold and the retrocochlear auditory pathway, may be used (16,45).

During the treatment, audiology monitoring should be done before every scheduled of cisplatin treatment or before every third cycle (or some recommend every cycle) of carboplatin (2). If there are any changes in hearing from the baseline, it must be confirmed by repeat testing within 24 hours (2,28,50,63). A significant shift in DPOAE is ≥ 6 dB amplitude reduction compared to the baseline SRO_{DP} (55). Confirmation of normal middle ear status using a tympanometer may be required to rule out middle ear pathology especially if abnormal otoscopic findings or DPOAE were found (4). Ototoxicity grading scales should be used to detect the severity.

Review of vestibulotoxicity associated with platinum-based chemotherapy (27) and systemic aminoglycosides (64) have been published, but none from RT. The questionnaire and bedside neurotologic assessment may be helpful (26,27,63). Bedside neurotologic examination mainly includes (I) test for vestibulo-ocular pathway or ocular motor tests, e.g., spontaneous and gaze-evoked nystagmus, head impulse test (Halmagyi-Curthoys test or head thrust test), head-shaking test, dynamic visual acuity (DVA) and (II) test for vestibulospinal pathway or posture and balance tests e.g., Romberg's test, Fukuda (Unterberger) stepping test (64,65). Objective vestibular function tests include electronystagmography (ENG) or videonystagmography (VNG) test, rotational (rotatory chair) test, computerized dynamic posturography, video head impulse test (vHIT), cervical- and ocular-vestibular evoked myogenic potentials (c-VEMP, o-VEMP) (27,64).

Changes from baseline of Dizziness Handicap Inventory (DHI) ≥ 18 points (66), of Tinnitus Handicap Inventory (THI) ≥ 20 points (67), or Hearing Handicap Inventory (HHI) ≥ 12 points (68) should be considered as significant (63).

Abnormalities of the bedside and objective vestibular test referred to general abnormal setting value, not from changing from the baseline (27,64). The most sensitive and appropriate for early detection of vestibulotoxicity is still a challenge, requires more evidence-based study (27). Complaints of auditory symptoms e.g., hearing loss, tinnitus, hyperacusis, aural fullness or vestibular symptoms e.g., dizziness, vertigo, imbalance, disequilibrium, oscillopsia, are usually present later than the changes of the objective tests (2,26,27).

Post-treatment auditory test frequency depends on the treatment modality that the patients received. For patients treated with cisplatin, carboplatin hearing tests should be done within one month of the last treatment and then every three months for one year. For patients treated with cranial radiation, the hearing test should be done within 1 month of the last treatment and then every 6 to 12 months for 10 years (2,28,55,69). Monitoring of auditory ototoxicity using a smartphone application or tablet-based technology has already reported but limited data (70-72).

No consensus exists for tinnitus or vestibulotoxicity monitoring frequency and monitoring tools (63) and no certain time indicated for audiovestibular tests before, during, or after the RT for NPC (2,28,55). The clinician may consider the application of cochleotoxicity monitoring protocols for chemotherapy or cranial radiation.

Once the ototoxicity was detected, the patient care team should consider starting appropriate actions to prevent progression and permanent damage, e.g., (I) offer alternative treatment option, (II) modify of the treatment regimen, (III) inform the patient and family, (IV) management of the detected disease or pathology, (V) auditory rehabilitation, (VI) vestibular rehabilitation (45,55,64).

The summary of the monitoring tools for cochleotoxicity and vestibulotoxicity are shown in *Table 4*.

Summary

Increased rate of successful chemoradiotherapy treatment increased the survival rate and prevalence of late toxicity in NPC survivors. Hearing loss commonly developed at speech frequencies later than at higher frequencies. Vestibular loss gradually deteriorates bilaterally. Most of the patients may not aware of the worsening of their audiovestibular symptoms. Once the treatment was planned, ototoxic monitoring should be scheduled. Clinicians should aware of the risk factors associated with increasing ototoxicity. The patient care team should promptly take an action once

Table 4 Ototoxicity monitoring tools

Tools	Cochleotoxicity	Vestibulotoxicity
Neurological examination	Pneumatic otoscopy	Vestibulo-ocular pathway: e.g., nystagmus, head impulse test, head-shaking test, dynamic visual acuity
	Tuning fork test	Vestibulospinal pathway: e.g., Romberg's test, Fukuda stepping test
Questionnaire	Tinnitus Handicapped Inventory	Dizziness Handicapped Inventory
	Hearing Handicap Inventory	
Objective tests	Pure tone audiometry	Electronystagmography (ENG) or videonystagmography (VNG) test
	High-frequency audiometry	Rotatory chair test
	Distortion product otoacoustic emission (DPOAE)	Computerized dynamic posturography
	Speech audiometry (speech reception thresholds, word recognition)	Video head impulse test (vHIT)
	Speech audiometry in quiet and in noise	Vestibular evoked myogenic potentials (VEMPs)
	Sensitive range of ototoxicity using PTA and HFA (SRO _{BEH})	
	Sensitive range of ototoxicity using DPOAE (SRO _{DP})	
	Speech audiometry in noise	
	Auditory brainstem response	
	Tympanometry	

the ototoxicity has been detected to prevent permanent damage to the hearing and balance system. Evidence-based of the ototoxicity emphasize mainly in cochleotoxicity after chemotherapy. Monitoring protocols and ototoxicity rating scales may be different among the centers according to available objective tests and limitations of the resources. Clinicians should consider the application of the protocol for the best monitoring outcomes. Successful of otoprotective studies have continuously proceeded. Increased tumor-controlled rate with a decreased rate of toxicity and minimizing medicolegal concern should be expected soon.

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