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Chemoradiotherapy-induced Cochlear Toxicity

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Abstract
Radiation-induced sensorineural hearing loss (RI-SNHL) is a progressive and irreversible complication of radiotherapy (RT) or chemoradiotherapy (CRT) of brain or head and neck tumors. Onset and progression times of RI-SNHL may broadly vary depending on the RT technique, dose, and concurrent or adjuvant usage of ototoxic medications, such as cisplatin. Characteristically the high frequencies (≥4 kHz) form the first affected range on a typical audiogram, which may be trailed by impairements in the lower hearing frequencies. RI-SNHL may adversely impact both the academic and social advancement in pediatric age and may deteriorate quality of life measures in all affected patients regardless of their age. Even if not eliminate all, in absence of a unequivocally proven medical treatment to avoid or alleviate the RI-SNHL, utilization of more advanced RT techniques, such as the intensity-modulated RT, and limiting the cochlea doses to ≤40-45 Gy for RT alone,<10 Gy for concurrent RT and cisplatin, and <10-12 Gy for stereotactic radiosurgery applications may demonstrate valuable in minimizing the risk of SNHL development. Furthermore, as reactive oxygen species (ROS) are the essential introductory causatives in RT-induced damage via activating the apoptotic cascade in cochlear hair cells, hopefully the development of novel radioprotective agents with the ability to lessen ROS production may prove beneficial in reducing the cochlear damage, and therefore, RI-SNHL, in near future.

Keywords: Cochlea, ototoxicity, radiotherapy, chemoradiotherapy, cisplatin, prevention.

Introduction

Radiotherapy (RT) or chemoradiotherapy (CRT) are well established integral part of definitive organ preservation or postoperative adjuvant treatment of head and neck cancers (HNC), and brain-, brainstem-, and skull base tumors and (1). Because of the significantly enhanced survival times with more effective local and systemic treatments, the late complications of RT and systematic chemotherapeutics have been noted to be more frequently manifested in these patients, such as the late ototoxcity. Progressive and irreversible sensorineural hearing loss (SNHL) is relatively the commonest and most debilitating treatment related ototoxicity type which is mainly caused by the damage to the cochlea (the organ of hearing and balance) and/or acoustic branch of the vestibulocochlear nerve, which are located in close proximity or right inside the RT field in most HNC and brain tumors.

Present manuscript aims to focus on the diagnosis, clinics, pathophsiology, radiobiology, and treatment and/or prevention maneuvers of radiation-induced SNHL(RI-SNHL) with specific empahasis on the preventive related measures including the use of sophisticated RT techniques and dose constraints to the cochlea.

Hearing Process in Brief

Recognizing the fact that it is undoubtedly more complex, the process of hearing is roughly divided into six basic steps:

1) To begin with, the sound waves approaching a particular side of the head travel along the external acoustic meatus and reach the tympanic membrane on that side.

2) The tympanic membrane collects the sound waves and vibrates in resonance to their frequencies between approximately 20 and 20,000 Hz. Vibration of tympanic membrane transfers the sound to the malleus, incus, and stapes bones and cause displacement of them in a vibrating manner, which in this way amplifies the incoming sound.

3) Because the liquids are not compressible and the rest of the cochlea is sheathed in bone, the stapes vibrating at the frequency of the sound arriving at the oval window creates pressure waves in the perilymph of the scala vestibuli.

4) The pressure waves created by the stapes travel through the perilymph of the scala vestibuli and scala tympani to reach the round window, where these waves distort the basilar membrane before reaching the round window of the scala tympani. The frequency of the sound determines the location of maximum distortion because of the regional differences in the width and flexibility of the basilar membrane along its length. Based on the laws of acoustical physics, the high frequency sounds with shortest wavelength vibrate the basilar membrane near the oval window, while the lower the frequency sounds with the longer the wavelength vibrates the farther regions of the basilar membrane, therefore determines the area of maximum distortion. Therefore, with these unique capabilities, it is imperative to note that the cochlea is an excellent frequency analyzer.

5) Hair cells are moved against the tectorial membrane by the vibrating zone of the affected basilar membrane, which prompts the displacement of the stereocilia with resultant opening of the ion channels in the plasma membranes of the hair cells of the spiral organ. The hair cells are depolarized by the influx of ions, leading to stimulation of sensory neurons by the release of neurotransmitters. In the spiral organ, the hair cells of are organized in several rows and are stimulated according to the intensity of the incoming sound. That, a very soft sound (less intense) stimulates only a couple of hair cells in a small portion of one row, while not only do these hair cells become more active but additional hair cells (first in the same and afterward in neighbouring rows) are stimulated as well, in parallel with the increments in the intensity of the incoming sound.

6) Lastly, the cell bodies of the bipolar sensory neurons that monitor the cochlear hair cells, which are located at the center of the bony cochlea (in the spiral ganglion), carry the information from the cochlea to the cochlear branch of vestibulocochlear nerve. Cochlear nerve than transfers the processed information to the cochlear nuclei of the medulla oblongata.From there, information ascends to the superior olivary nucleus of the pons and both inferior colliculi of the midbrain, where a number of responses to acoustic stimuli including the auditory reflexes that involve skeletal muscles of the head, face, and trunk are coordinated. Before reaching the cerebral cortex and the individual's awareness, ascending auditory sensations synapse in the medial geniculate nucleus of the thalamus. Than the projection fibers deliver the information to the auditory cortex of the temporal lobe over cortical labelled lines. Therefore, the auditory cortex contains a map of the spiral organ, implying that the low and high frequency sounds activate distinctive zones of the auditory cortex.

Radiobiological Aspects of RI-SNHL

Radiation is the emission and propagation of energy through space or a material medium. Simply, there are two kinds of radiation, namely particle- and electromagnetic radiation. Particle radiation is defined as the energy propagation by traveling corpuscles which has a definite rest mass and within limits have a definite momentum and defined position at any instant. Electromagnetic radiation, first described by Maxwell, implies for the mode of energy propagation such as light waves, heat waves, radio waves, microwaves, ultraviolet rays, and ionizing radiations including the X- and γ-rays.

The energy of ionizing radiation is conveyed in the form of photons, also called quantum, where quantum represents for the smallest unit of the energy of electromagnetic radiation. Principally, ionizing radiation may be classified as directly or indirectly ionizing. All of the charged particles are directly ionizing and carry adequate energy that is sufficient to cause direct biologic or chemical changes by disrupting the atomic

structure. While, indirectly ionizing X-and γ-rays do not themselves lead to direct biologic or chemical changes in the tissue through which they pass, instead they give up their energy to produce fast-moving charged particles that in turn able to produce damage in the absorbing media.

At high energy levels, such as cobalt-60 units or linear accelerators, Compton process is the predominant interaction type between the incoming photon and the target tissue, in which the energetic photon ejects a loosely bound outer electron from the attacked atom by imparting a part of its energy to the electron. Low linear energy transferring X- and γ-rays mainly produces their actions via these fast moving electrons: indirect action of radiation, and constitute approximately 2/3 of its all actions on tissue. In this interaction mode, radiation interacts with intra and extracellular molecules, particularly the H_2O molecules which are the most abundant molecules in the living tissues. Consequences of this reaction lead to production of highly reactive free radicals (mainly hydroxyl radicals) with the diffusing capacity of relatively short distances in the cell. When the hydroxyl radical reach the deoxyribonucleic acid (DNA) it binds to the DNA and cause double-strand breaks. If not rapidly and accurately repaired, these breaks result in mitotic cell death, induction of apoptotic response by activation of p53 (guardian of the cell), or lengthened cell cycle arrest. The faith of the preferred pathway will depend on the cell type, severity of damage, and the integrity of p53. Although the rapidly proliferating tissues, such as the mucosa or skin, may react quickly and renew the injured tissue totally, in tissues with no self-proliferation capacity or functional progenitor units the result will be the total loss of organ function, such as the hair cells of the organ of Corti or the neurons of the spiral ganglion (2-4).

The damage initiated by free radicals has been postulated to propagate by the production of cytoplasmic reactive oxygen species (ROS) in the presence of O_2, which are particularly damaging to the oxygen-rich mitochondria (5). Although the radiation-induced excess ROS production is comparably lower than those produced during normal oxidative metabolism processes and adds only a little to the total quantity, yet, it may reach levels sufficient enough to disrupt homeostasis and create oxidative stress in the cell (6). Accessible evidence demonstrated the additional stimulation of the nitric oxide synthase by radiation and formation of peroxynitrite anions as a result of its reaction with superoxide dismutase (7). Peroxynitrite anions are excessively reactive nitrogen species (RNS) which further damage cell membranes and DNA. Therefore, continuous production of ROS and RNS alone or together may promote and deepen the radiation-induced cell damage at long term (7).

In vitro evidence suggests that the non-proliferative cochlear hair cells die most likely by the activation of RT-induced apoptosis (8). RT-induced apoptosis may occur in two separate ways: p53 dependent and p53 independent pathways. In the p53 dependent apoptosis, sensation of the DNA injury activates the p53 with resultant cell cycle arrest to facilitate DNA repair process in tolerable injuries or activation of apoptotic pathways if the damage is irreversibly beyond the repair capacity (9). In one of the rare reports investigating the apoptosis in auditory hair cells, Low et al. (8) studied the post-RT apoptosis and ROS production in immature mice auditory hair cells, and showed that ROS production was increased in just 1h after the RT while 72 h was needed to detect p53 activation. This finding is important by demonstration of the increased ROS production as a function of exposed dose and as a triggering factor for activation of p53 dependent apoptotic processes in the cochlear hair cells. The second probable cochlear damage pathway is the p53 independent pathway (sphyngomyelin-ceramide pathway), which becomes evident 24 h after RT-induced DNA damage in epithelial cells as a dose-dependent response involving the interaction of ROS with the cellular plasma membranes (10). Nonetheless, given their profoundly specialized and non-proliferative state, it is unlikely that the outer and inner hair cells of the organ of Corti or neurons of the spiral ganglion exhibit this pathway as a response to RT. On the other hand, the sphyngomyelin-ceramide pathway may be activated in the vascular endothelial cells of the stria vascularis with resultant p-53 independent apoptosis in the inner and outer hair cells, at least in the range of high-dose single fraction RT.

In summary, accessible radiobiologic data suggests that the main cells affected after fractionated RT are the inner and outer cells of the organ of Corti and to some degree the neurons of spiral ganglion, with p53 dependent apoptosis being the main and established pathway of cell death, and therefore development of RI-SNHL.

Pathophysiology of RI-SNHL

Despite the fact that Girden and Culler were the first to exhibit noteworthy increments in the hearing thresholds of irradiated dogs in 1933 (11), yet, the earliest experimental studies on the functions of the inner

ear go back to 1905 with Ewald's first observations which demonstrated the diminished vestibular functions of irradiated pigeons. In another striking early investigation published in 1958, Kozlov revealed a 3.9 to 9.1 dB decline in the hearing of irradiated guinea pigs involving the all frequencies between the 0.5 to 8.0 kHz (12).

An essential drawback of early experimental animal studies was that the animals were commonly exposed to single fraction large doses of radiation which might have been associated with morbidities far beyond the currently utilized conventionally fractionated clinical RT protocols. Single fraction large dose RT has been estimated to be much more lethal than the equivalent amount administered over time using appropriately fractionated protracted schemes (13). Recently, using a novel model mimicking human exposures, Miller et al. compared the effects of RT (70.75 Gy over 25 fractions) versus cisplatin-alone versus their combination in guinea pigs (14). Proposing the RT as the main causative of SNHL, the authors reported that the 5 of 6 animals in the RT alone arm developed severe SNHL in at least one ear in contrast with no significant SNHL in the cisplatin-alone arm.

Radiation-induced Sensorineural Hearing Loss

Radiotherapy either alone or combined with chemotherapy constitutes the backbone of multidisciplinary treatment of HNC, skull base, brain, brainstem, and cerebellopontine angle tumors both in adult and pediatric patients. As a result of the intricate and interconnected anatomy of this region, uni- or bilateral cochlea often unavoidably dwells within the high-dose region of conformal RT plans. Even though the cochlear dose may be reduced to some extent by using more sophisticated intensity-modulated RT (IMRT) and respecting the pre-specified dose constraints, yet, cochlea may still receive significant doses in many cases.

RI-SNHL, which manifests months or years after the completion of the RT in nearly 50% (range: 4-90%) of all patients, is probably the most serious RT-induced late toxicity of the head and neck region except for the tissue necrosis (15-17). RI-SNHL may occur as early as within 3 to 24 months after completing RT (median: 1.5-2 years), which is suggested to be relatively shorter in single fraction large dose SRS (median: 4 months) than the hypo- or conventionally fractionated RT schemes (18). Some studies also reported that hearing reduction/loss may suddenly occur just after the RT as a result of mechanistically different acute reactions (19,20). One proposed mechanism explains the acute and sudden hearing loss as a consequence of the compression of the cochlear artery caused by SRS-induced edema (20). Another explanatory mechanism for the acute hearing deterioration proposes that the rapid formation of the post-RT free radical ions create a triggering effect for vasospasm of the stria vascularis which in turn dramatically decreases the cochlear blood flow (21) and cause hearing reduction/loss depending on the extent of ischemia.

Radiation-induced vascular endothelial damage is one of the causes accused of SNHL advancement (22,23). Animal and human investigations have indicated alterations such as bleeding at inner ear spaces and edema at membranous labyrinth, internal and external hair cell loss at organ of Corti, and atrophic degeneration of the stria vascularis, spiral ganglion cells, and cochlear nerve (24,25). Inflammation and edema prompted by RT may likewise damage the cochlear nerve in the narrow bone canal (26). Human temporal bone studies uncovered that patients who received cisplatin, RT, or both, ended up with a decrement of spiral ganglion cells alongside the loss of internal and external hair cells and atrophy of stria vascularis (27).

RI-SNHL can have sudden or progressive character. Sudden SNHL (SSNHL) can be defined as SNHL of at least 30 dB in three consecutive frequencies occurring over three days or less (28), while progressive SNHL is described as a hearing loss ≥30 dB which shows ≥10 dB regression at any frequencies during the consecutive 3-monthly audiometric follow-ups (29). Severe SNHL described as ≥20 dB difference between the irradiated and unirradiated ears by some authors (30,31); while some others accept ≥10-15 dB loss as the critical cut-off for severe loss (32,33). Though the clinical stage may settle in 2 years for permanent SNHL (>15 dB), yet, this interval may lengthen to 3 to 4 years for more severe (>30dB) SNHL (34). Nevertheless, in studies with longer follow-up periods, such as 13 years or more, SNHL is specified to have a stable characteristic rather than being progressive (35).

Scoring Systems for Hearing Loss

Ototoxicity is a complication induced by antibiotics, diuretics, chemotherapeutics, and RT; which diminishes hearing function and quality of daily life measures as a result of damaged hearing structures including the vestibular, cochlear or conductive bony structures (36,37). Regarding the RT-induced SNHL,

usually, the insult first affects the cells responsible for the high-frequency hearing (≥4 kHz) at basal segments of the cochlea and then propagates to the cells responsible for the low-frequency hearing (<4 kHz) at the apical region. While the loss in the speech range frequencies (<4 kHz) prompts troubles in understanding the daily public conversations, typical high frequency losses (≥4 kHz) cause impaired recognition and differentiation of sounds at higher frequencies, including the natural sounds such as bird crowing or bee buzzing, and sounds of musical instruments. Since the hearing function is critical for social relations, communication, education, work-life, and expression of feelings the detection and grading of objective hearing loss is mandatory for the timely interventions and healthy maintenance of a qualified lifestyle. Therefore, objective audiometric evaluations before and during the RT or CCRT, maintenance chemotherapy, and follow-up periods is essential. Although the recommended frequency range for hearing evaluations involves the frequencies between 0.25-8.0 kHz, explicit considerations may be required in some adult risk groups and pediatric patients.
The most frequently used hearing loss scoring systems are as depicted in Tables 1 to 5.

Table 1. CTCAEv4 and ASHA scoring criteria

CTCAEv4 (adult)	Audiograms evaluated at 1, 2, 3, 4, 6 and 8 kHz
	Grade 0: No hearing loss.
	Grade 1: 15-25 dB threshold shift on two consequent frequencies or subjective alteration while no Grade 1 threshold shift is present in at least one ear
	Grade 2: >25 dB threshold shift on two consequent frequencies in at least one ear
	Grade 3: >25 dB threshold shift on three consequent frequencies in at least one ear
	Grade 4: Severe bilateral hearing loss (≥80 dB at 2kHz)
ASHA	**No:** No hearing loss.
	Yes: ≥20 dB threshold shift at any frequency rate or ≥10 dB threshold shift on two consequent frequencies

CTCAEv4, Common Terminology Criteria for Adverse Events version 4; ASHA, American Speech-Language-Hearing Association

Table 2. Chang and Brock scoring criteria

Chang Score	Threshold of hearing loss (dB)	Brock Score	Threshold of hearing loss (dB)
0	≤20 dB at 1,2 and 4 kHz	**0**	<40 dB at all frequencies
1a 1b	≥40 dB in between 6-12 kHz >20 and <40 dB at 4 kHz	**1**	>40 dB at 8 kHz
2a 2b	≥40 dB at ≥4 kHz >20 and <40 dB at<4 kHz	**2**	≥40 dB at ≥4 kHz
3	≥40 dB at ≥2 kHz	**3**	≥40 dB at ≥2 kHz
4	≥40 dB at ≥1 kHz	**4**	≥40 dB at ≥1 kHz

Table 3. Toxicity criteria according to the Radiation Therapy Oncology Group scoring system

Grade	Toxicity
0	No difference from the beginning
1	Mild external otitis with erythema, pruritus, secondary to dry desquamation not requiring medication. Audiogram unchanged from baseline
2	Moderate external otitis requiring topical medication/serous otitis media/hypoacusis on testing only

3	Severe external otitis with discharge or moist desquamation/symptomatic hypoacusis/tinnitus, not drug related
4	Deafness

Table 4. Late stage ear toxicity according to LENT/SOMA score

	Grade 1	Grade 2	Grade 3	Grade 4
Subjective Pain Tinnitus Hearing	Seldom Seldom Minimal loss, no difference in daily basis	Sometimes, tolerable Sometimes Difficulty of understanding low-volume conversations	Severe Persistent Difficulty of understanding high-volume conversations	Intolerable Persistent Complete deafness
Objective Skin Hearing	Dry desquamation <10 dB loss at ≥1 frequencies	External otitis 10 - 15 dB loss ≥1 frequencies	Superficial ulcer 15 - 20 dB loss at ≥1 frequencies	Necrosis >20 dB loss at ≥1 frequencies
Management Pain Skin Hearing Loss	Non-narcotic medication Lubricant	Non-narcotic medication Drop-antibiotic	Narcotic medication Tympanic membrane Hearing aid	Intravenous narcotics Surgery

Abbreviation: LENT/SOMA, Late Effects of Normal Tissue/Somatic Objective Management Analytic

Table 5. Gardner Robertson Hearing Classification

Grade	Hearing Level	Pure tone average (dB)	Speech discrimination score (%)
I	Good to excellent	0-30	70-100
II	Serviceable	31-50	50-69
III	Non-serviceable	51-90	5-49
IV	Poor	91- maximum	1-4
V	None/deaf	Non-testable	0

Albeit each scoring system provides valuable objective information about the hearing status, yet each system has its pros and cons compared to other systems as described below. For example; the Common Terminology Criteria for Adverse Events Version-4 (CTCAEv4) and American Speech-Language-Hearing Association (ASHA) (Table 1) are lacking to assess hearing loss at ultra-high frequencies. In this regard, CTCAEv4 is particularly noted to insufficiently report the degree of hearing loss and its clinical importance in pediatric patients. Though the RT-induced hearing loss initially occurs at ultra-high frequencies, CTCAEv4 ignores these frequencies due to its assessment rate restricted to the frequencies between 1 to 8.0 kHz. So also, gradual increments in hearing loss cannot be evaluated with ASHA scoring system as the frequency range of hearing loss is not specified. Even though the RI-SNHL is chronic type ototoxicity, the Radiation Therapy Oncology Group (RTOG) criteria likewise don't assess chronic ototoxicity and preferably

used for evaluation of acute ototoxic events for retrospective investigations (Table 3). The Late Effects of Normal Tissue/Somatic Objective Management Analytic (LENT-SOMA) criteria (Table 4) provides a prospective evaluation of late-stage toxicity. However, LENT-SOMA is primarily used for chemotherapy studies and is noted to be insufficient in the assessment of quantitatively small but clinically significant changes, and as a noteworthy disadvantage, it does not clarify the mainly affected compartment(s) of the cochlea (38). The classification proposed by Gardner and Robertson is another commonly used classification system, but again this system has the disadvantage of being useful in assessment of hearing preservation after surgery or SRS (39).

Further complicating the situation, wide variability between the affected patients populations' regarding the patient age, total and per fraction dose of RT, RT technique, concurrent use of ototoxic antibiotics or chemotherapeutics, and scoring methodologies render it difficult to compare different studies evaluating the RT-induced ototoxicity. Thus, more objective scoring systems determining the affected compartment of the hearing apparatus and evaluating the severity of acute and chronic ototoxic events in pediatric and adult cancer populations are urgently required.

Risk Factors for RI-SNHL

The frequently referred risk factors for RT- or CRT-induced SNHL are summarized in Table 6.

Table 6. Risk Factors for Post-RT SNHL Development

Treatment related factors	Patient related factors	Tumor related factors
High total RT dose High marginal dose* Cisplatin SRS versus FSRT Conventional RT (versus IMRT) High dose-rate Fraction dose >2 Gy Furosemide Aminoglycosides	Advanced age Neurofibromatosis type-2 Diminished basal hearing Male gender Post-RT serous otitis Hypersensitivity to RT or cisplatin	Unfavorable tumor localization (Nasopharynx, skull base, etc.) Large tumor size High-location lymph nodes Cystic or solid type tumour

*For stereotactic radiosurgery

Abbreviations: RT: Radiotherapy; SRS: Stereotactic radiosurgery; FSRT: Fractionated stereotactic radiotherapy; IMRT: Intensity-Modulated radiotherapy

In general, the impact of patient's age on SNHL development is debated. Albeit many researchers proposed the geriatric age as a risk factor (40-42), Zuur et al. proposed that the magnitude of hearing loss was significantly higher in younger patients than their older counterparts (43). In this manner, young patients with good basal hearing levels will experience more severe hearing loss after RT or CRT which will lead to lower hearing threshold levels years after the completion of treatment. But, suggesting a radiation hypersensitivity of the cochlea, presence of age-related degenerative cochlear changes in elderly patients were also proposed as a worsening factor SNHL actuated by RT or CRT (44).

To our best information, presently the most grounded risk factors for RT-induced SNHL are total and per fraction RT doses exposed by the cochlea. Moreover, it has been reported that the RI-SNHL incidence and severity were exhibiting gradual increments paralleling with the total RT dose, particularly with cochlear doses beyond 45 Gy (45-48). The outcomes of the large retrospective analysis incorporating 325 head-neck cancer patients reported by Bhandare et al. clearly demonstrated that the total cochlear RT dose was independently associated with increased 5-year SNHL risk in multivariate analysis (3% with ≤60,5 Gy versus 37% with 60,5 Gy; >p<0.0001) (48). Although the radiation dose limits for cochlea is usually set at <45 Gy, yet, various investigators recommend <35-40 Gy and <30 Gy for adult (49,50) and pediatric patients (51), respectively, while others set the critical threshold at ≥47-55 Gy (50, 53, 58, 59). Differing significantly from these traditional dose limits Hermann et al proposed the 20-25 Gy range as the significant cut off for ≥15 dB change in hearing thresholds in 50% of the irradiated patients (52).

The influence of fractionation (conventional versus hyper-fractionation) is debated for the conventional dose per fraction range of 1.2 to 2 Gy (48). In some vestibular schwannoma studies, it was noticed that the hearing function was more effectively spared with fractionated SRS than the single-dose SRS protocols (53,54). However, regarding the 8-year hearing preservation rates, Meijer et al. found no statistically significant difference between single- and multi-fractionated SRS schemes in 129 vestibular schwannoma patients treated with one of the 5 × 5 Gy, 5 × 4 Gy, 1 × 10 Gy, or 1 × 12.5 Gy SRS conventions (55). To date, no exact latency interval has been proposed for post-RT SNHL development, yet accessible proof recommends that compared to single-fraction SRS regimes, fractionated SRS may extend the latency interval from median 4 months to 18-24 months (38,44).

It is well-perceived that the concurrent use of chemotherapy with RT, particularly the cisplatin enhances the locoregional disease control and survival outcomes in many tumor sites including the head and neck (56,57). Cisplatin, as a strong cytotoxic and radio-sensitizing agent, targets the cellular DNA via the production of reactive oxygen radicals and triggering of the apoptotic pathways, which are also common for RT-induced cell killing (58,59). On animal researches, the ototoxic effects of both radiation and cisplatin are shown by targeting similar structures of the cochlea (external and internal hair cells, stria vascularis and nerve ends) (60,61). Various studies demonstrated that the cisplatin per cycle doses of ≥50 mg/m^2 or cumulative doses ≥400 mg/m^2 was associated with approximately 33% SNHL development (42,43,62-64). Hitchock et al. constructed a model to predict dose-dependent hearing loss for RT or cisplatin-based chemotherapy either alone or in combination. For patients only receiving RT, no significant hearing loss was found at doses to the cochlea of <40 Gy. Patients receiving 100 mg/m^2 or 40 mg/m^2 of cisplatin chemotherapy had an estimated +21.5 dB and +9.5 dB hearing loss at 8.0 kHz with low radiation doses (10 Gy), which rose to +38.4 dB and +18.9 dB for high radiation doses (40 Gy). In contrast, patients who received <40 Gy cochlear dose and no chemotherapy did not experience any notable hearing loss (58). In a seminal investigation, Rademaker et. al evaluated the auditory toxicity associated with dose- and schedule- intensive cisplatin/gemcitabine chemotherapy in non-small-cell lung carcinoma patients and demonstrated that hearing loss after cisplatin therapy occurred mainly at high frequencies and at cisplatin dosages over 60 mg/m^2, which was more pronounced when cisplatin was given once every 2 weeks (64). Theunissen et al. compared the SNHL incidences after RT versus CRT in a systematic review comprising 21 studies (1). Although the wide range of SNHL incidence rates made it impossible to draw any conclusions on the severity of RT- and CRT-induced ototoxicity, yet, the authors reported that the incidence rates of meaningful SNHL after RT and CRT were 0% to 43% versus 17% to 88%, respectively. In this review, the adverse factors that influenced the risk of SNHL were identified as the higher RT dose to the cochlea, longer follow-up time, advanced patient age, diminished baseline hearing level, and higher cisplatin dose.

Considering the aforementioned facts, it is imperative to determine pre-treatment hearing condition and risk factors to determine the true incidence of SNHL in patients undergoing RT or CRT. Supporting this notion, it has been repeatedly emphasized that >50% of all nasopharyngeal cancer patients present with conduction type hearing loss secondary to serous otitis media (65-67). It should be remembered that the toxic effects of cisplatin may progressively continue for years even when used as a single agent without RT (68,69). To affirm, when compared to the cisplatin naive population, serum cisplatin levels were 30 times higher in the patients' cohort treated with cisplatin after 8 to 75 months of its administration (70). Moreover, another study demonstrated that cisplatin was detectable in the plasma even after 20 years of its utilization (71).

Prevention and Treatment of Sensorial Neural Hearing Loss

The cumulative ototoxicity risk of concurrent use of RT and cisplatin is without no doubt much higher than the risk of either treatment alone. Further complicating the problem, a recent study by Clemens et al. showed that the meaningful hearing loss rates were 45% in cisplatin-, 17% in carboplatin-treated, and 75% in childhood cancer survivors (N=451) who received both agents (72), and the risk was increased by a factor of 2.3 when patients were co-treated with furosemide in absence of RT.

Since cisplatin is the indispensable component of many anticancer treatment protocols, many preclinical investigations have been performed to develop agents exerting otoprotective actions against cisplatin. But, unfortunately, just a couple of them could move into clinical studies. Studies of amifostine's protective effect against cisplatin-induced ototoxicity in children with hepatoblastoma and germ cell tumors failed to show otoprotection (73,74). Nevertheless, the trial reported by Fouladi et al. in 97 average-risk medulloblastomas revealed that the amifostine use was associated with a significantly reduced requirement for hearing aid in at

least one ear because of grade 3 ototoxicity (14.5% versus 37.1%; P=0.005) at 1-year of treatment (75), which was recently confirmed by a retrospective analysis (76). Sodium thiosulfate is another antioxidant tested for its otoprotective actions. Preclinical studies and initial phase 1-2 trials indicated that sodium thiosulfate has a potential otoprotective effect, with most extreme viability occurring particularly when administered 4 to 8 hours after cisplatin (77-80). Considering the tumor protective actions, further pharmacokinetic evidence demonstrated the 6 hours interval as the safe timing for the delayed administration of sodium thiosulfate (81,82). The SIOPEL-6 was a phase 3 trial designed to investigate whether delayed sodium thiosulfate administration would reduce the incidence and severity of the cisplatin-induced hearing loss. The authors randomized 109 children who had standard-risk hepatoblastoma to one of cisplatin alone or cisplatin plus sodium thiosulfate arms (83). The primary endpoint was the absolute hearing threshold measured by pure-tone audiometry. The incidence of SNHL of grade ≥1 was significantly lower in the cisplatin-sodium thiosulfate group as compared to its cisplatin-alone counterpart (33% versus 63%; P=0.002), indicating a 48% lower incidence of hearing loss with delayed sodium thiosulfate administration with no negative impact on the survival outcomes (83). N-acetylcysteine, a precursor to the antioxidant glutathione with strong free radical scavenging actions, is one of the few agents proposed to exhibit otoprotection against cisplatin-induced ototoxic actions (84,85). In an in vitro study, Feghali et al. demonstrated a dose-dependent otoprotective effect of N-acetylcysteine against cisplatin on both auditory neurons and hair cells (86). Sarafraz et al conducted a double-blind randomized trial to compare the otoprotective impact of transtympanic injections of N-acetylcysteine and dexamethasone in 60 cisplatin-treated patients (87). Hearing acuity was evaluated with pure tone audiometry. Altogether, 114 transtympanic infusions were performed (57 in each group). The authors reported that no significant changes in auditory thresholds were recorded in the ears treated with N-acetylcysteine, dexamethasone-treated patients exhibited a significant decrease of auditory thresholds at the 8.0 kHz frequency band (P = 0.001). Albeit additional proof is required, based on the accessible favorable data, both the sodium thiosulfate and N-acetylcysteine have received a Food and Drug Administration orphan status for the indication of otoprotection (88).

Although many agents have been tested for their otoprotective functions, to our best information, no protective measure gained evidence-based acceptance to date. Therefore, radiation-initiated SNHL ought to be treated as idiopathic SSNHL with supportive measures such as steroid administration and hyperbaric oxygen therapy, hearing aid usage, or cochlear implantation in appropriately selected cases. In this context, it is imperative to spare cochlea by using more sophisticated RT techniques, such as the intensity-modulated RT, and obey the proposed dose restrictions for cochlea. In brief, as the best effort, the cochlear dose ought to be kept ≤40-45 Gy for conventionally fractionated RT and <10 Gy for concurrently administered RT plus cisplatin regimens. For SRS, the cochlear dose should not exceed 10-12 Gy to minimize the risk for hearing loss.

Conclusion

RI-SNHL is usually a late-onset progressive and irreversible treatment complication which may involve one or both ears relying upon the treatment methodology chosen. As a rule, RI-SNHL initially affects the high frequencies which may spread to lower frequencies. At present, in spite of the fact that amiphostine, N-acetylcysteine, and sodium thiosulphate exhibited some viability in prevention of cisplatin-induced SNHL, yet the proof isn't sufficiently robust to suggest their utilization as an otoprotector for patients experiencing RT or CRT. Thusly, in absence of effective medications with strong otoprotective or treatment functions, the best otoprotective measure is the utilization of IMRT with obeying the recommended cochlear dose constraints together with avoidance of ototoxic drugs, such as aminoglycoside antibiotics. We recommended ≤40-45 Gy and <10 Gy cochlear doses for conventionally fractionated RT alone and concurrently administered RT plus cisplatin regimens. In like manner, the cochlear dose should not exceed 10-12 Gy to minimize the hazard for hearing loss after SRS. Future effort should focus on the identification of at-risk individuals and development of highly selective and efficient otoprotectors with no tumor promoting actions.

Declarations
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