SYSTEMATIC REVIEW

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Clinical aspects of hearing loss associated with cisplatin therapy – a review

Felician Chirteş[1]

Abstract:
Introduction: Cisplatin is a well known platinum-based chemotherapeutic agent used for the treatment of diverse malignant tumours.
A frequent side effect of cisplatin therapy is ototoxicity.
Material and methods: Experimental, clinical studies and reviews from the English language medical literature concerning ototoxicity were selected either from PubMed or printed medical journals, pointing out cisplatin-induced ototoxicity. Molecular mechanisms, clinical audiological and histological marks of cisplatin-induced ototoxicity as well as current experimental and clinical strategies for prevention or treatment of hearing loss were reviewed.
Results and discussion: A wide range of otoprotective molecules and efficient strategies against cisplatin-induced hearing loss proved to be helpful in experimental studies whereas only dexamethasone settled a slight otoprotective effect in a clinical study.
Conclusion: There is no currently available treatment for cisplatin associated hearing loss and further research is required for future therapeutic options.

Keywords: *cisplatin-induced hearing loss, otoprotection, intratympanic therapy, systemic therapy, gene therapy.*

INTRODUCTION

Although synthesized already since 1845 by Peyrone and named Peyrone's salt, cisplatin was used clinically in oncologic therapy for head and neck, lung, bladder, cervical, ovarian, testicular, gastrointestinal cancers, as well as malignant gliomas and metastatic cancers such as melanoma, mesothelioma, and those of the prostate and breast [1] only in the late 1960s. Irreversible neurosensorial hearing loss which affects both ears symmetrically, high frequencies in the first place followed by low, speech range frequencies in a dose related, cumulative fashion is one of its major side effects.

Pre-existing afflictions like hypoalbuminemia, anaemia, renal failure, noise-induced hearing loss or by risk factors like therapy with loop diuretics, aminoglycoside antibiotics, radiotherapy fields which includes the inner ear, extreme ages (very young or very old), duration and dose schedule of cisplatin infusion, genetic factors can favour cisplatin-induced hearing loss. The average incidence of cisplatin-induced hearing loss is about 62% [2]. Cisplatin-induced tinnitus is another frequent side effect. These phenomena may occur within hours to days

[1] Military Hospital, Cluj Napoca

after cisplatin administration. As subsequent multiple cisplatin regimens for the control of cancer may be necessary, side effects should be prevented or treated without reducing the efficacy of the antitumoral mechanisms.

MATERIAL AND METHODS

Outer hair cells are the main target for cisplatin ototoxicity which progresses from the third to the first row, and to some extent, to inner hair cells of the or gan of Corti in the basal turn of the cochlea followed by alterations in sensorial cells situated in the apex.

Supporting cells, marginal cells of the stria vascularis and the spiral ligament are also afflicted by cisplatin ototoxicity [3]. Vestibular organs and spiral ganglion cells may also suffer from cisplatin ototoxicity, especially in experimental conditions [4]. In patients with cancers of the head and neck whose communication is already impaired, the ensuing hearing loss is very disabling and cause for depression. [5].

The creation of reactive oxygen species and depletion of antioxidant glutathione and its regenerating enzymes as well as increased rate of lipid peroxidation, oxidative modifications of proteins, nucleic acids damaged by Caspase system activation [2] and S-nitrosylation of cochlear proteins and resulting apoptosis of inner ear cells stand for the molecular mechanisms of cisplatin-induced hearing [6].

Cochlear tissues fight the oxidative stress by means of antioxidant defence systems including glutathione, glutathione reductase, superoxide dismutase and catalase. Potassium uptake and secretion in the stria vascularis also might be disturbed by cisplatin administration, leading to impairment of the function of outer and inner hair cells in the organ of Corti, with alteration of the endocochlear potential and subsequent hearing loss [7].

Measurements of hearing loss by means of pre-treatment and follow-up serial audiologic tests are used to assess the extension of ototoxicity due to cisplatin therapy. Experimentally, histological examinations could point out injuries due to cisplatin administration [8]. Audiologic tests include pure tone (normal frequency and extended high frequency range), speech and impedance audiometry, auditory brainstem responses and Distortion Product Otoacustic Emissions (DPOAEs) testing.

DPOAEs reflect early injuries to outer hair cells in the organ of Corti thereby allowing monitoring and early detection of cisplatin ototoxicity during cancer treatment [9,10]. Cisplatin early ototoxic effects cause hearing impairment in the high frequencies at 6 kHz, 8 kHz and above as measured by conventional or extended high-frequency pure tone audiometry [11]. Multiple doses of cisplatin worsen hearing, ultimately affecting the speech frequency range (500 - 4000 Hz). Since DPOAEs measurement is based on the integrity of outer hair cells which is affected by cisplatin therapy before elevation of auditory threshold as measured by pure tone audiometry.

DPOAE testing is more sensitive than the latter for the detection of cisplatin-induced ototoxicity.

Moreover, the results provided by DPOAEs, as an objective testing, are not influenced by the ability of the deteriorating cancerous patient to respond to the sound stimulus [9]. In small children who undergo cisplatin administration for cancer treatment and who cannot cooperate for pure-tone testing because of their younger age and poor cognitive ability, either soundfield behavioural testing or DPOAEs could be performed [12].

In experimental animals, auditory brainstem response recordings mirror hearing loss after cisplatin treatment [3].

Histological examinations of inner ear after cisplatin administration reveals destruction primarily of outer hair cells and to some extent inner hair cells and associated nerves, degeneration of the vestibular organs, stria vascularis edema and detachment of the myelin sheath of the spiral ganglion cells [4]. The damage is especially noticed in the high frequency region of the cochlea (i.e. the basal turn) probably due to a base to apex gradient of the cisplatin ototoxicity [14]. Immunostaining detected tumour

necrosis factor-alpha (TNF-α) and other inflammatory cytokines (IL-8, IL-6) in the outer hair cells, stria vascularis, spiral ligament and spiral ganglion neurons in cisplatin exposed cochlea [3].

Intravenous injection of cisplatin is followed by strong binding of the alkylating agent to the plasma proteins rendering a large non-active part of it.

The barrier systems in the cochlea, the blood-perilymph barrier, separating blood from perilymph, and the intrastrial fluid-blood barrier, separating blood from endolymph also influence the pharmacokinetics of cisplatin therapy [15]. The amount of free chemotherapeutic agent reaching targets in the cochlea is responsible for the ototoxic effect and consequent hearing loss. High frequency audiometric thresholds are initially affected. When doses in excess of 100 mg/m^2 are used, the hearing impairment may progress from high frequencies to involve the middle frequencies. Reducing the total amount of cisplatin by limitation of the total dose per cycle, dose intensity and the cumulative dose would diminish the antitumour effect, which is not desirable.

Various otoprotective compounds have been tested both in experimental animals and humans. If given systemically, they should be non-toxic, must attain efficient concentrations in the inner ear to protect labyrinthine tissues from cisplatin ototoxicity and should not hamper the anti-tumour effect of cisplatin. Higher concentrations of otoprotective molecules can be achieved by intratympanic administration.

This latter route provides direct access of the protective agents to inner ear structures while avoiding systemic side effects and interference with the anti-neoplastic activity of cisplatin [16].

Experimental studies

Several otoprotective molecules and strategies against cisplatin-induced ototoxicity have been tested in experimental animals.

Hyperbaric oxygen therapy consisting of intermittent inhalations of 100% oxygen at a pressure higher than 1 atm is used as adjuvant therapy in pathological processes like soft tissue infections, radiation injury, gas gangrene and decompressive disease.

Tissue hyperoxygenation through plasma dissolved oxygen was succesfully tested in guinea pigs as a protective agent against cisplatin ototoxicity.

Otoacoustic emissions recordings following hyperbaric treatment and scanning electron microscopy examination proved the efficacy of otoprotection by hyperbaric oxygen therapy after cisplatin administration.

The study confirmed that cisplatin induces dose-dependent cochlear alterations consisting of cellular lesions and significant hair damage in outer hair cells. Analysis of anatomical changes in cochlear outer hair cells indicated signs of otoprotection against cisplatin in animals treated with hyperbaric oxygen therapy although in functional studies the distorsion product otoacoustic emissions were absent reflecting a certain degree of hearing loss, most probably reversible and related to experimental artifacts.

The study concluded that hyperbaric oxygen therapy has otoprotective effects against cisplatin induced ototoxicity. However, further studies are needed to test other effects of high pressure oxygen on the cochlea [17].

The effect of epigallocatechin gallate (EGCG) on the transcription factor STAT1, an important mediator of cell death was investigated by another study. STAT1 phosphorylation is involved in both hair cells and support cells transformation after experimental exposure of mouse utricle to cisplatin.

EGCG proved its efficiency as an otoprotective agent against cisplatin ototoxicity due to its inhibition of STAT1. The failure of EGCG to provide protection against cisplatin in STAT1-deficient mice also supported the hypothesis [18].

Near total preservation of otoacoustic emissions after cisplatin therapy was possible when lactate was injected intratympanically in guinea pigs treated with ototoxic levels of cisplatin, as shown in former studies [19]. A further study was conducted to prove the Ringer solution otoprotective effect against cisplatin ototoxicity when injected intratympanically, before

intraperitoneal cisplatin administration since lactate is a part of Ringer solution and it has the smallest molecular weight among other antioxidants which facilitates transport across the round window membrane. The molecular protective mechanism is based on the enzyme lactate dehydrogenise located in the mitochondria of outer hair cells. The conversion of lactate to pyruvate in the presence of the enzyme leads to the formation of nicotinamide adenine dinucleotide (NADH) which is a natural antioxidant that may be involved in fighting against oxygen reactive species resulted at cellular level after cisplatin therapy. Electron microscopy examinations of guinea pig cisplatin-insulted inner ears pre-treated with lactate showed partial preservation of outer hair cells stereocilia, more significant at mid frequencies (2000-4000 HZ) but not statistically significant at higher frequencies. The study used auditory brainstem responses recordings which is a more sensible method than otoacoustic emissions testing, a fact that explains the differences in otoprotective effect reported by previous studies.

The same study investigated the otoprotective effect of intratympanic N-acetylcysteine injections as well as its systemic diffusion following the administration.

The results showed that high concentration of intratympanic N-acetylcysteine is not reliable for otoprotection against cisplatin ototoxicity since it caused more middle and inner ear damage than cisplatin alone. Yet, N-acetylcysteine did not diffuse systemically when applied to the middle ear. This was confirmed by high-performance liquid chromatography testing of blood samples taken from the venous system of the experimental animals after intratympanic injections of N-acetylcysteine. This latter outcome proves that the intratympanic route of administration would be safe and prevent inactivation of antitumoral effect of cisplatin by binding between the thiol moiety of N-acetylcysteine and the platinum-containing molecule of the chemotherapeutic drug [20].

Most of the existing studies deal with exogenous administration of antioxidants. Pharmacological activation of intrinsic defence mechanisms against oxidative stress in the inner ear caused by cisplatin therapy also proved helpful as showed by an experimental animal study using systemic administration of thiamine pyrophosphate (TPP). Thiamine pyrophosphate functions as coenzyme for peroxisomes, being a crucial factor for energy metabolism, antioxidation and myelinization of nerve cells. Its intraperitoneal injection increased the level of natural antioxidants like glutathione and antioxidant enzymes (superoxide dismutase, glutathione peroxidase and glutathione reductase) and reduced the content of malonildialdehyde, an indicator of lipid peroxidation following increased levels of oxygen reactive species resulted from cisplatin toxicity. The histological evaluation of cochleas harvested from TPP treated animals showed preservation of the morphology of the organ of Corti and outer hair cells, and no destruction of spiral ganglion cells and stria vascularis following cisplatin therapy [4].

Sertraline, an antidepressant with neuroprotective effects in rats was also studied for its presumed otoprotective effect against cisplatin-induced ototoxicity [6]. The selective serotonin reuptake inhibitor has antioxidant effects, stimulates neurogenesis and increases antiapoptotic protein levels [21].

Oral administration of sertraline in cisplatin-treated rats has prevented hearing loss above 5000 Hz, in a statistically significant manner, as documented by distortion product otoacoustic emissions recordings.

Besides, sertraline would be beneficial to depressed patients due to their cancerous disease and their deteriorated communication abilities [5].

The otoprotective effect of systemic histone deacetylase inhibitor sodium butyrate was proved in an experimental single dose model of cisplatin ototoxicity.

A sensitive assay of the functional state of outer hair cells after systemic cisplatin insult on the cochlea was provided by distortion product otoacoustic emissions testing. The systemic administration of the otoprotective agent avoided the side effects of the more invasive tympanical local route of administration.

Moreover, sodium butyrate did not interfere with the tumoricidal effect of cisplatin providing both protections from reactive oxygen species and a certain degree of antitumor activity according to previous reports. The protective effect against oxidative stress and the cell division inhibition and subsequent anticancer activity follow acetylation of different cell proteins, including histones. The experiment's weak point is the single dose of cisplatin model whereas in clinical practice cisplatine in multiple doses [22].

One animal study showed the efficacy of short interfering RNA in preventing cisplatin ototoxicity by reducing the expression of NOX3, the unique isoforme of NADPH oxidase involved in the generation of reactive oxygen species, in outer hair cells, spiral ganglion cells and stria vascularis in the rat. Auditory brainstem responses certified reduced threshold shifts in cisplatin treated animals who received transtympanic NOX3 and RNA. Since cisplatin administration has been previously associated with upregulation of NOX3 in the inner ear, Nox3 is thought to be a major source of free radicals in the cochlea following cisplatin exposure. The resulting free radicals initiated the inflammatory process in the cochlea by activating signal transducer and activator of transcription-1 (STAT1), followed by activation of p53 and the increase in inflammatory mediators like TNF-alpha and interleukin-1ß [23]. A single transtympanic injection of RNA has atenuated cisplatin ototoxicity by suppressing inflammation in a dose-related manner. It hampered cisplatin-induced auditory brainstem responses threshold shift and higher doses allowed for complete morphological preservation of outer hair cells as proven by scanning electron microscopy examinations of the rat cochleas [24].

Minocycline is a tetracycline derivative that proved its partial efficacy among various strategies that have been devised in experimental settings to prevent cisplatin ototoxicity. The anti-inflammatory and neuroprotective properties of minocycline have been previously reported. The biochemical mechanism involves caspase-1 and caspase-3 inhibition, which decreases the amount of interleukin-1 and prevents apoptosis. The protective effect of minocycline has been tested both in cisplatin treated cell cultures and in experimental animals which underwent cisplatin intraperitoneal therapy after systemic administration of the otoprotective agent.

Cell viability assays showed that minocycline had a protective effect against cisplatin toxic action. Yet, minocycline failed to protect cells at higher concentrations of cisplatin. Recordings of auditory brainstem responses and evaluation of the scanning electron microscopy sections of inner ears harves ted from minocycline plus cisplatin treated animals indicated a partial preservation of the function and morphology of the outer hair cells as compared to those from animals treated with cisplatin alone [25].

Intraperitoneal erdosteine effect on cisplatin-induced ototoxicity in a guinea pig model was also studied. Erdosteine is a thiol derivative with well-known antioxidant properties due to its active sulfhydryl groups following liver first-pass metabolism.

Living animals underwent pre and posttreatment auditory brainstem responses measurements while outer hair cell counts were analyzed by scanning electron microscopy of the cochlea removed from euthanized animals. Despite the study's limitations (i.e. minimal number of animals included, lack of enzymatic activity detection for the main antioxidant enzymatic systems of the inner ear), the results outlined the systemic administration of erdosteine as a promising therapeutic strategy for cisplatin-induced ototoxicity [26].

Intratympanic dexamethasone prevents hearing loss in a frequency related manner as reflected by a first murine model for cisplatin-induced ototoxicity.

Evoked brainstem responses audiometry indicated that 8 kHz and 16 kHz stimulus elicited responses in cisplatin plus dexamethasone treated mice while high frequency stimulus (32 kHz) perception was affected. Apparently, cisplatin had deleterious effects on outer and inner ear cells situated in the basal turn of the cochlea despite intratympanic administration of protective dexamethasone [27].

Further experimental studies supported the finding

that cisplatin exerts its damaging effect in a base to apex gradient, lower frequencies being spared for long. Higher doses of dexamethasone also seem to be more protective than lower doses. Moreover, lower doses of cisplatin allow the naturally present antioxidants to annihilate the resulting reactive oxygen species, explaining the spontaneous hearing threshold recovery even in the absence of protective dexamethasone administration [28].

Dexamethasone diminishes the tumoricidal activity of cisplatin, hencing the preference for intratympanic administration which avoids this unwanted effect. Down-regulating apoptosis genes in tumor cells are responsible for this common side effect of systemic steroid therapy [29]. An experimental study conducted on cisplatin treated guinea pigs asserted the safety of intratympanic dexamethasone based on audiologic and histologic results.

Auditory brainstem responses testing, optic microscopic and scanning electron microscopic examinations of cochlea showed no significant differences between intratympanic dexamethasone-treated animals and saline-treated controls. Dexamethasone administered intratympanicaly proved efficacious in protecting the labyrinth against cisplatin-induced ototoxicity as shown by reduced auditory brainstem responses threshold shifts and unaltered histological inner ear structures. The molecular mechanisms involve increased expression of Na/K channels and aquaporins in the endolymphatic sac and the tissues around the endolymphatic spaces. The study's results also suggest that giving the intratympanic dexamethasone one hour before the cisplatin administration provides the best protection (total protection) against the ototoxic insult by the alkylating agent compared to dexamethasone injections one day prior to cisplatin administration (partial protection) [14].

In order for the dexamethasone to exert a protective effect against cisplatin ototoxicity, the timing of administration of the two drugs should be highly synchronized so that the peak concentration of dexamethasone in the perilymph should be correlated with the peak concentration of the chemotherapeutic agent, according to another study [2].

Otoprotection with dexamethasone against age-related cisplatin-induced hearing loss was investigated in a guinea pig model following observations that persons older than 65 account for more than half of the newly diagnosed malignancies.

Hearing loss due to the aging process shares the same cause (i.e. oxidative stress) with hearing loss due to ototoxic chemotherapeutic agents.

A single dose of cisplatin was administered intraperitoneally in old mice preceded and followed by dexamethasone injected intratympanically to counteract the cisplatin toxic effect on inner ear hair cells. Pre and post treatment auditory brainstem responses were recorded to evaluate hair cell function. The results of the study pointed out that no synergistic action between age related hearing loss and cisplatin-induced hearing loss exists since threshold shifts were smaller in older animals than those in young mice.

Another finding of the study was that the protective effect of dexamethasone against cisplatin-induced ototoxicity was a function of stimulus frequency in old mice. Susceptibility to otoprotective effect of dexamethasone was higher in mid to basal cochlear regions (at and above 24 kHz) in old mice , whereas

in young mice, dexamethasone bestowed more protection in apical regions of the cochlea (at 16 kHz and below). Age-related changes of the mechanism of distribution of dexamethasone in scala tympani perlymph after round window membrane application in guinea pigs seem to account for the frequency dependent otoprotective effect [30].

Intratympanic dexamethasone did not protect against cisplatin-induced ototoxicity in a multidose cisplatin ototoxicity mouse model. The study was prompted by typical clinical protocols of cancer treatments which require administration of multiple, smaller cisplatin doses, exerting their curative effect through cumulative dosing. Contrary to previous experimental studies, the mice received five doses of cisplatin throughout five days, mimicking the cumulative exposure seen in malignant tumours treatment.

Intratympanic dexamethasone was administered on the same days as the intraperitoneal cisplatin. The results mirrored by auditory brainstem responses threshold measurements demonstrated continued change in hearing thresholds several weeks after cisplatin exposure and no protective effect of intratympanic dexamethasone against cisplatin ototoxicity [31].

An experimental study focusing on systemic administration of steroid for protection against cisplatin-induced ototoxicity showed no otoprotection following several days' prophylaxis with a high dose dexamethasone treatment. Only a slight decrease of TNF-alpha expression in the cochlea was demonstrated by imunohistochemical staining of anatomical samples harvested from systemic cisplatin plus dexamethasone treated animals. Dexamethasone also seemed to protect stria vascularis from morphological alterations, probably owing this effect to higher concentrations of steroid in the lateral cochlear wall following increased cochlear flow and a naturally highly vascularised stria vascularis.

Still, a functional otoprotective effect of systemic dexamethasone against cisplatin-induced hearing loss was not observed [3].

Among naturally occurring molecules, Rosmarinic acid, a water-soluble polyphenolic compound extracted from Dansam-Eum, was tested for its protective effect against cisplatin-induced ototoxicity in laboratory settings. The results of the study showed that Rosmarinic acid inhibited cisplatin induced caspase-1 activation providing protection against stereocilia loss in the primary organ of Corti explants [32].

Another natural remedy, the Maytenus ilicifolia aqueous extract, was evaluated for its possible otoprotection in guinea pigs. Despite the well-known South America plant's antioxidant effects (due to the presence of flavonoids and alkaloids), functional tests did not demonstrate any protective action on the cisplatin exposed cochlea. Yet, the extract improved the clinical status and weight of guinea pigs and diminished mortality after cisplatin exposure [33].

Resveratrol, a polyphenol found in grape skin and seed, has anti-oxidant, neuroprotective and dose dependent antiapoptotic properties [34]. Recent experimental research pointed the preventive effect of resveratrol against cisplatin induced ototoxicity.

An in vitro study on House Ear Institute-Organ of Corti 1 cell line showed that resveratrol in low doses prevented ototoxicity mainly influencing apoptotic gene expression but proved cytotoxic effect in high doses [34]. Two other studies showed conflicting results. Thus, high doses of oral resveratrol administered to mice seem to enhance cisplatin ototoxicity[35] whereas systemic administration of lower doses of resveratrol provided significant protection to the cochlea against cisplatin [36].

Clinical studies

Intratympanic dexamethasone was clinically tested for its otoprotective effect in patients afflicted with neoplastic diseases for which the treatment protocol included cisplatin. Intratympanic dexamethasone is a current remedy for idiopathic sudden sensorineural hearing loss and Meniere disease [37].

Intratympanic administration of drugs avoids significant systemic side effects. The intratympanic route also provides higher concentrations of drug in the inner ear fluids and prevents significant interference between dexamethasone, which is known to reduce efficacy of chemotherapeutic agents, and cisplatin.

Patients enrolled in the study underwent unilateral intratympanic dexamethasone administration prior to every cisplatin treatment session, with the contralateral ear used as a control. Serial follow-up audiometry and distortion product otoacoustic emissions testing were performed to check the functional state of both study and control ears. The statistically significant results showed that intratympanic dexamethasone is slightly protective against cisplatin-induced hearing loss at 6000 Hz and decreases the outer hair cells dysfunction in the frequency range of 4000 to 8000 Hz. The conclusion of the study is that intratympanic dexamethasone has minimal effect towards reducing cisplatin ototoxicity. Optimal concentrations of dexamethasone and a

perfect timing of administration would be necessary to prevent hearing loss after cisplatin therapy [2].

Patients with head and neck cancer undergoing cisplatin therapy were given transtympanic L-N-Acetylcysteine to check its otoprotective effect.

Thiol compounds either directly bind cisplatin or act as free radical scavengers. Based on that, their intratympanic administration was suggested to avoid the decrease of oncologic effectiveness of cisplatin and to reduce the oxidative stress caused by it.

Intratympanic L-N-Acetylcysteine was well tolerated by patients receiving multiple doses of cisplatin as part of their oncologic treatment. The relation between dose and otoprotection was not taken into account. Higher concentrations may have yielded better otoprotection. The study protocol required the L-NAC injection to be approximately 1 hour before systemic administration of cisplatin, for the sake of better timing. The outcome of the pure tone audiometry testing at 1 and 2 months after the last cycle of cisplatin showed that L-N-Acetylcysteine was overall not significantly otoprotective. Still, hearing loss was reduced in two patients out of eleven who completed the study. The study protocol had several challenges like the difficulty in maintaining high enough concentrations of aqueous solution of L-N-Acetylcysteine in the middle ear due to the technique of administration and the different initial hearing thresholds due to preexisting hearing loss [38].

Among systemic otoprotective molecules for preventing cisplatin-induced hearing loss, amifostine, a phosphorylated aminothiol designed to protect against radiation damage, was known to counteract the toxic effect of different anticancer treatments without interfering with the tumoricidal effect. Although significant protection of amifostine against haematological toxicity after high dose carboplatin therapy in a child with medulloblastoma was reported [39], a clinical study considering systemic administration of amifostine failed to prove any otoprotective effect against cisplatin-induced hearing loss in a group of paediatric patients treated with cisplatin associated with other chemotherapeutic agents [40].

OTOPHARMACOGENETICS

The well-isolated inner ear organ makes it prone to targeted genetic therapies. Viral or non-viral gene vectors can be delivered through a transtympanic route without the risk of dispersing them and reaching other tissues with subsequent undesirable genetic alteration. Long term effects after single administration, cellular selectivity and replacement of genetically flawed nucleic acid sequences are the main benefits of gene therapy. Common viral vectors include herpes simplex virus, recombinant adenoassociated virus, recombinant adenovirus, adenovirus, used to amplify the expression of targeted genes. Cells are infected with the vectors (transfection) which transfer genes whose expressed proteins influence important processes like growth, oxidative stress and apoptosis. Chemical transfection can also be achieved with plasmid vectors. Short interfering RNA can be used to shut down target genes.

Among inner ear target genes dealt with by the gene therapy studies are ATOH1 (Math1), CAT (catalase), SOD1 (Cu/Zn superoxidedismutase), SOD2 (Mn superoxide dismutase), BDNF (brain-derived neurotrophic factor), HGF (hepatocyte growth factor), GJB2 (gap junction protein), BclxL (B-cell lymphoma-extra large), FGF2 (basic fibroblast growth factor). The gene therapy modifies the synthesis of a wide range of proteins including neurotrophic factors (NTF3, GDNF), apoptosis mediators (XIAP,BCL2), oxidases (NADPH, NOX1, NOX3, NOX4), an antioxidant response regulator (Nfe2l2), a cytoprotective enzyme (HO-1), a copper transportes (Ctr1), a nonselective cation channel (Trpv1) and a protein Otospiralin (Otos).

Cisplatin-exposed tissues can benefit from genetically induced up-regulation of neurotrophic factors, inhibition of apoptosis and generation of endogenous antioxidant enzymes.

Experimental animal studies and in vitro experiments show the efficacy of gene therapy for cisplatin-induced ototoxicity. Clinical applications require further studies regarding safety, immunogenicity and consequences of genetic manipulation [41].

Another strategy to avoid cisplatin-induced hearing loss would be the pretreatment genotyping to find out patients at risk for the ototoxic effect of cisplatin [42]. Genetic variants (polymorphism) of different protein systems (Tiopurine S-methyltransferase, Catechol-O-methyl transferase, Glutathione-S-transferase with its subclasses M1/T1/ P1, Megalin) can stand for the interindividual variability in cisplatin ototoxicity [43].

RESULTS AND DISCUSSION

43 publications were reviewed concerning prevention or treatment of cisplatin induced ototoxicity.

Publications were devised in either experimental or clinical studies. All researches emphasize the importance of reactive oxygen species in cisplatin induced ototoxicity. The hearing loss following cisplatin treatment affects principally the high frequencies, extending to speech range frequencies as multiple doses of cisplatin worsen hearing.

Experimental studies supported the efficiency of hyperbaric oxygen therapy, epigallocatechin therapy and intratympanic lactate. The latter two therapies provide exogenous antioxidants while pharmacologic activation of endogenous antioxidants by means of intratympanic thiamine pyrophosphate was consistent with higher levels of natural antioxidants.

Oral sertraline, besides its otoprotective effect against cisplatin induced ototoxicity, also has therapeutic value concerning the depression occurring frequently in oncologic patients. Sodium butyrate proved its efficiency against cisplatin induced hearing loss in a monodose cisplatin model. Yet, in clinical practice the patient receives multiple doses of ciplatin. The production of endogenous radicals of oxygen species was reduced after intratympanic administration of short interfering RNA which reduces the expression of NOX3 in the cochlea. Minocycline appeared to be efficient only at low doses of cisplatin, while systemic erdosteine showed promising results. Dexamethasone in experimental studies combined efficiency against cisplatin induced ototoxicity with preservation of the tumoricidal activity of cisplatin. When older mice were treated, the dexamethasone was more otoprotective at higher frequencies compared to experiments including younger subjects. Rosmarinic acid also proved to be otoprotective while the Maytenus ilicifolia aqueous extract was not. Resveratrol had contradictory effects, systemic low doses and in vitro administration preventing ototoxicity, whereas high oral doses seem to enhance cisplatin ototoxicity.

Also, there were some experimental studies which showed inefficiency of intratympanic NAcetylcysteine and intratympanic and systemic dexamethasone. N-Acetylcysteine, in addition having a damaging effect on middle and inner ear structures.

Clinical studies proved a minor otoprotective effect of intratympanic dexamethasone and no effect of systemic amifostine and intratympanic LN-Acetylcysteine.

New perspectives are brought about by genetic therapy using viral vectors and genotyping to anticipate interindividual variability in cisplatin ototoxicity.

CONCLUSION

New strategies are required for hearing loss prevention and treatment during cisplatin therapy for cancer besides optimization of old ones. The intratympanic route of administration and the gene therapy are among the most promising perspectives in further experimental and clinical studies.

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