

Effect of N-Acetylcysteine on Cisplatin Toxicity: A Review of the Literature

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Abstract: N-acetylcysteine (NAC) is a membrane-permeable cysteine precursor capable of enhancing the intracellular cysteine pool, enhancing cellular glutathione (GSH) synthesis, and thus potentiating the endogenous antioxidant mechanism. Late administration of NAC after cisplatin has been shown in different in vivo studies to reduce the side effects caused by various toxicities at different levels without affecting the antitumor efficacy of platinum, improving total and enzymatic antioxidant capacity and decreasing oxidative stress markers. These characteristics provide NAC with a rationale as a potentially effective chemo protectant in cisplatin-based therapeutic cycles. NAC represents a potential candidate as a chemoprotective agent to decrease toxicities secondary to cisplatin treatment. It suggests that it could be used in clinical trials, whereby the effective dose, timing, and route should be adjusted to optimize chemoprotection. This review provides an overview of the effect of NAC on cisplatin toxicity, a drug widely used in the clinic in adults and children.

Keywords: cisplatin, toxicity, chemo protectant, oxidative stress, antioxidant

Introduction

Childhood cancer is a major contributor to the mortality rate in the world.¹ While cancer treatments have improved survival rates, the toxic response to treatment, and the formation of free radicals have caused more deaths than the disease.² Cancer treatment is currently surgery, chemotherapy, and radiotherapy; chemotherapy is multi-pharmacological; numerous medications can impact the antioxidant status during therapy.³ Cisplatin is a widely used chemotherapy drug due to its effectiveness and broad range of applications in the clinic. The main mechanism behind the antineoplastic activity of cisplatin is its ability to crosslink with DNA, which inhibits transcription and replication. However, the clinical use of cisplatin is limited due to its severe toxicity (nephrotoxicity, ototoxicity, neurotoxicity) and dose-dependent side effects.⁴ Antioxidants, such as N-acetyl cysteine, are said to prevent this toxicity. N-acetylcysteine (NAC) is a precursor of L-cysteine acetylated and reduced glutathione. NAC is an over-the-counter, safe, and well-tolerated dietary supplement.^{5–7} This review summarized evidence for NAC as a protective agent against cisplatin toxicity.

It's important to consider the role of antioxidants in the impact of excessive oxygen consumption on the body. Reactive oxygen species (ROS) can cause damage to proteins, cell membranes, DNA, and RNA, potentially leading to the development and advancement of cancer.^{8–12} Antioxidants are crucial in neutralizing free radicals and preventing oxidative damage. They work by donating electrons to free radicals, interrupting chain radical reactions, and deactivating metals. The body's natural antioxidant system includes enzymatic antioxidants like superoxide dismutase SOD, catalase (CAT), glutathione peroxidase (GPx), and Thioredoxin (Trx), as well as hydrophilic and lipophilic antioxidants. By decreasing cellular damage parameters such as oxidative stress and DNA mutations, antioxidants help protect against the harmful effects of ROS^{13,14}

Oxidative stress arises from the imbalance of prooxidants and antioxidants, leading to biomolecule changes and disease development. Cancer cells escalate ROS production due to mitochondrial dysfunction, metabolic alterations, and genetic mutations, activating protumorigenic signaling pathways. While moderate ROS levels promote cell functions, high levels induce cell death. Cancer cells enhance antioxidant capacity but are insufficient against high ROS levels and supports protumor signaling.^{15–19}

Cisplatin

Cisplatin, chemically referred to as cis-diamminedichloroplatinum (CDDP), was first synthesized by M. Peyrone in 1844. The scientific community largely ignored this compound until 1965, when Rosenberg found that the electrolyte product of platinum electrodes could impede the cell division of *Escherichia coli*. This was later identified as CDDP.^{4,20,21}

It was the first platinum compound approved by the FDA for the treatment of cancer in 1978, under the name cisplatin; since then, it has been used as a chemotherapeutic agent in different types of cancers, including bladder, breast, cervix esophagus, head and neck, ovarian, prostate, small cell and non-small cell lung, stomach, testicular cancers, Hodgkin's and non-Hodgkin's lymphomas, melanoma, mesothelioma, multiple myeloma, neuroblastoma, sarcomas, medulloblastoma and osteosarcomas.^{20–22} Cisplatin is a compound consisting of a central platinum (Pt) atom coordinated with two ammonia (NH₃) ligands and two chloride (Cl) ion ligands, forming a planar quadrilateral.²²

The absorption of cisplatin is facilitated through the copper transporter 1 (CTR1) and organic cation transporters (OCTs).^{20,21} Cisplatin is resistant to hydrolysis outside cells because of the high concentration of chloride ions in the blood (around 100 mM). After entering cells, cisplatin undergoes a slow hydrolysis process, forming cationic mono aqua and di aqua complexes. This occurs due to the relatively low concentration of chloride ions, which ranges from 4 to 22 mM. The complexes [Pt(NH₃)₂Cl(OH₂)]⁺ and [Pt(NH₃)₂(OH₂)₂]²⁺ are derived from cisplatin and are known for their high reactivity towards cellular targets. These complexes, consisting of mono and di-aqua molecules, are prone to hydrolysis and can react rapidly.^{4,21,22} (DNA is the main biological target).^{4,20} This product, which is hydrolyzed, can react with proteins' sulfhydryl groups and nucleic acids' purine bases.^{20,22,23} Cisplatin attaches to the reactive N7 center on purine residues, creating crosslinking complexes. These complexes comprise 90% 1.2 intracatenary d(GpG) adducts and 10% 1.3 intracatenary d(ApG) adducts. These mechanisms are responsible for the cytotoxicity of cisplatin, along with monofunctional adducts and interstrand crosslinks.^{4,20}

The effects of cisplatin-induced adducts and crosslinks include DNA unwinding, bending, replication, and transcription inhibition, which can lead to DNA strand breaks, impaired cell division, and initiation of pro-apoptotic pathways.^{22,23}

Furthermore, CP can raise ROS levels, leading to mitochondrial dysfunction and promoting lipid peroxidation (LPO). CP can also activate the intrinsic apoptosis pathway by triggering mitochondrial permeabilization, releasing cytochrome C (cyt C), and stimulating caspase expression. Additionally, it can activate the extrinsic apoptosis pathway through the induction of Fas receptor signaling. It has been reported that CP can sensitize cancer cells to cell death by altering intracellular calcium levels.^{21,24}

Cisplatin Toxicity

Cisplatin has certain limitations in dosage and clinical application due to its tendency to cause toxic side effects. The most common are nephrotoxicity, ototoxicity, neurotoxicity, gastrointestinal toxicity, and hematological toxicity. While less frequent, other side effects include cardiotoxicity, hepatotoxicity, retinal toxicity, inappropriate antidiuretic hormone syndrome, hypersensitivity reactions, and reproductive toxicity, which may still occur in some cases.^{4,20,21,24}

Nephrotoxicity

Approximately 25–35% of adults experience nephrotoxicity.²⁵ and 70% of pediatric patients during therapeutic cycles.²⁶ Various factors, including elevated levels of ROS, mitochondrial dysfunction, inflammation, DNA damage, and induction of apoptosis, can cause renal toxicity.²⁷ Cisplatin mainly accumulates in the proximal and distal tubules of the kidneys, causing epithelial cell death and impairing tubular reabsorption. This activates the tubuloglomerular feedback mechanism and, together with tubular obstruction, reduces glomerular filtration.²⁸

One proposed mechanism for activating inflammatory responses involves inflammasomes containing the pyrin domain 3 (NLRP3) of the Toll-like receptor 4 (TLR4) and NLR family, which are pattern recognition receptors. The activation of nuclear

factor- κ B (NF- κ B) triggers the expression of NLRP3 and pro-interleukin (IL)-1 β (pro-IL-1 β). NF- κ B can be activated by different stimuli like lipopolysaccharide binding to TLR4 and ROS. Caspase-1 activation mediated by NLRP3 results in the cleavage of pro-IL-1 β and pro-IL-18, which are now known to play a role in Cisplatin-induced nephrotoxicity.²⁹

Ototoxicity

Cisplatin therapy often leads to permanent sensorineural hearing loss, which is a common complication,³⁰ between 40% and 80% of adults and at least 50% of children are left with permanent hearing loss.^{31,32} Cisplatin-induced hearing loss is essential because it affects the quality of life and later affects childhood access to speech and spoken language development. Language and communication are fundamental to psychosocial development, cognition, learning, and literacy.³³

Cisplatin ototoxicity is caused by multiple mechanisms,^{32,34} such as the production of reactive oxygen species, depletion of the antioxidant glutathione and its regenerative enzymes, increased lipid peroxidation rate, oxidative modifications of proteins, nucleic acid damage through activation of the caspases system, S-nitrosylation of cochlear proteins, and the resulting apoptosis of inner ear cells.^{32,35}

Long-term stepwise retention has been demonstrated with each cycle of platinum treatment in the cochlea after chemotherapy,^{31,36} damaging hair cells essential for maintaining hearing and spiral neurons, supporting cells, and vascular veins.³⁷ Thus, three cochlear regions are implicated in CP toxicity: the organ of Corti, spiral ganglion neurons, and the vascular stria.³¹

Neurotoxicity

Platinum-based chemotherapy often causes neurotoxicity, which reduces the effective dose and may lead to treatment discontinuation.³⁸ Cisplatin-induced peripheral neuropathy (Cis-PN) is a type of nerve damage that affects the sensory nerves in the hands and feet. It can cause a symmetrical distribution of symptoms known as “glove and stocking distribution”, which may also extend to the elbows and knees. It is associated with cumulative doses above 300–350 mg/m².³⁹ The drug is linked to adverse effects in 30–50% of patients who complete the course, causing debilitating symptoms in 10% of them.^{40–42}

Cis-PN causes numbness, tingling (paresthesia), burning, pain, reduced vibrational sensitivity in the fingers and toes, and decreased ankle reflexes.³⁸

In the peripheral nervous system, the sensory neurons in the dorsal root ganglion (DRG) are the primary site where cisplatin accumulates. This vulnerability can be attributed to several factors, including the lack of a blood-brain barrier (BBB), a lower amount of detoxifying glutathione, and specific membrane transporters called organic cation transporters (OCTs).^{43,44} Neurotoxicity caused by cisplatin has been linked to damage in mitochondrial and nuclear DNA.⁴⁵

Glutathione Synthesis and Functions

Glutathione (GSH) is a detoxifying agent in cells and one of the central mechanisms by which ROS are removed.⁵ The tripeptide, γ -L-glutamyl-L-cysteinyl glycine, is found in all mammalian tissues at 1 to 10 mM levels. It serves several vital functions, including antioxidant defense, xenobiotics detoxification, cell cycle progression, apoptosis regulation, cysteine storage, redox potential maintenance, immune function modulation, and fibrogenesis.⁴⁶ GSH, found inside cells, is produced from three amino acids: cysteine, glutamine, and glycine. The formation of γ -glutamyl cysteine and glycine, crucial components of GSH, is made possible by the enzyme glutamate-cysteine ligase (GCL) and the catalyst glutathione synthetase (GSS). GSS facilitates the reaction between γ -glutamyl cysteine and glycine, which ultimately results in the formation of GSH.⁴⁷

Cysteine has the lowest concentration of the mentioned precursors, which limits the rate of GSH synthesis during oxidative stress.⁵

N-Acetyl Cysteine

NAC is a man-made version of the natural amino acid L-cysteine.⁵ It is a thiol, membrane-permeable cysteine precursor capable of enhancing the intracellular cysteine pool, releasing thiols from proteins through disulfide cleavage, thereby increasing GSH levels and enhancing GSH-dependent detoxification activity of H₂O₂ by its antioxidant enzymes (its glutathione peroxidase and thioredoxin).⁴⁷

NAC is a commonly prescribed medication for treating acetaminophen (paracetamol) overdose. It replenishes the depleted GSH stores in hepatocytes during detoxification. Additionally, NAC has been found to have mucolytic properties, which means it can break down disulfide bonds in mucus glycoproteins, reducing viscosity.^{5,48–50}

The chemical structure consists of a sulfhydryl functional group (-SH) plus an acetyl group (-COCH₃) attached to the amino group (NH₂).^{51–53} Thiols (RSH) can be oxidized by radicals and act as electron-pair donors.⁵³ NAC has direct antioxidant properties because its free thiol group can interact with reactive oxygen and nitrogen species like hydroxyl radical (-OH), nitrogen dioxide (-NO₂), carbon trioxide ion (CO₃⁻), and thiyl radical (RS[•]), as well as nitroxyl (HNO) which is the reduced and protonated form of nitric oxide (-NO).⁵⁴

When reacting with species such as superoxide radical anion (O₂⁻), hydrogen peroxide (H₂O₂), and peroxynitrite (ONOO⁻), relatively slower reactions take place.^{51,53} However, O₂⁻ generated within cells is rapidly converted to H₂O₂ by local SOD, the substance can transform into water through a reaction catalyzed by either CAT or GPX. In the case of GPX, the process involves the oxidation of GSH to glutathione disulfide, which is then converted back to GSH by glutathione reductase, thioredoxin, and glutaredoxin.⁵

Likewise, NAC is an effective reducing agent of protein disulfides through the classical thiol-disulfide exchange mechanism. An S_N2 reaction mechanism involves the attacking NAC thiolate binding to the central sulfur of the disulfide in a single step, releasing the exiting thiol (R'SH), a capacity to restore systemic reserves of small thiols and reduce SH groups of proteins, regulating redox conditions as an antioxidant mechanism.⁵⁰

The SH group in NAC is a mild Lewis base, which makes it highly reactive with mild Lewis acids such as various toxic metals. The high effectiveness of NAC against toxic metals with mild Lewis acid properties is related to its stable binding to the SH group, producing inactive complexes. The formation of these complexes inside cells prevents the toxic binding of metals to the Cys-SH protein, while their extracellular production blocks the cellular uptake of metals.^{55,56}

Chemoprotection by N-acetylcysteine frequently results from the inactivation of primary toxicants or reactive electrophiles that arise as metabolites or lipid peroxidation products. The most toxic lipid oxidation products are α , β -unsaturated aldehydes such as acrolein, crotonaldehyde, and 4-hydroxy-2-nonenal (4HNE). The toxicity of these carbonyl compounds is caused by their very high reactivity with protein-SH groups through Michael's addition at the β -carbon of the double bond (R-CH=CH-CHO). The SH group of NAC rapidly forms Michael adducts with α , β -unsaturated aldehydes, which prevents their conjugation to proteins and the resulting toxic effects.^{55,57}

In addition to its antioxidant effect, NAC has an anti-inflammatory effect.^{58,59} N-acetylcysteine has been shown to decrease IL-6 levels in hemodialysis patients. TNF- α and IL-1 β have also decreased in mouse models treated with n-acetylcysteine. N-acetylcysteine inhibits the activation of redox-sensitive nuclear factor kappa B, which stimulates the expression of proinflammatory genes at times of oxidative stress, releasing many inflammatory cytokines.⁶⁰

In the case of cisplatin, as mentioned earlier, a lower chlorine concentration is found at the intracellular level; the chloride ions in cisplatin are replaced by water molecules, forming the cationic complexes mono-aqua and di-aqua,²⁰ species with a much higher avidity for nucleophilic sites on macromolecules, including DNA and proteins. The reactivity of aqueous species is modulated by the level of available molecules with free thiol groups, as in the case of NAC, thiol-containing molecules have high avidity for aqueous cisplatin species, preventing their binding to other cellular targets, mechanism underlying the highly effective cytoprotective properties of NAC, over those of other antioxidants²⁸ (Figure 1).

The antioxidant properties of NAC may be attributed to the following mechanisms:

- It has a direct antioxidant effect on specific oxidative species.⁵⁰
- The ability to act as a precursor of cysteine enhances cellular GSH synthesis and potentiates the endogenous antioxidant mechanism as an indirect antioxidant effect of NAC.⁵⁴
- The compound can break disulfide bonds and restore thiol stores, which help regulate the redox state.⁵⁰
- The ability of the free thiol of NAC to bind to mono-aqua and di-aqua cation complexes, preventing their binding to other cellular targets.²⁸
- The conversion of thiols derived from NAC into hyperactivated thiols (hydropersulfides) serves as direct oxidant scavengers and protective coatings for critical protein thiols in metabolism.⁵ (Table S1)

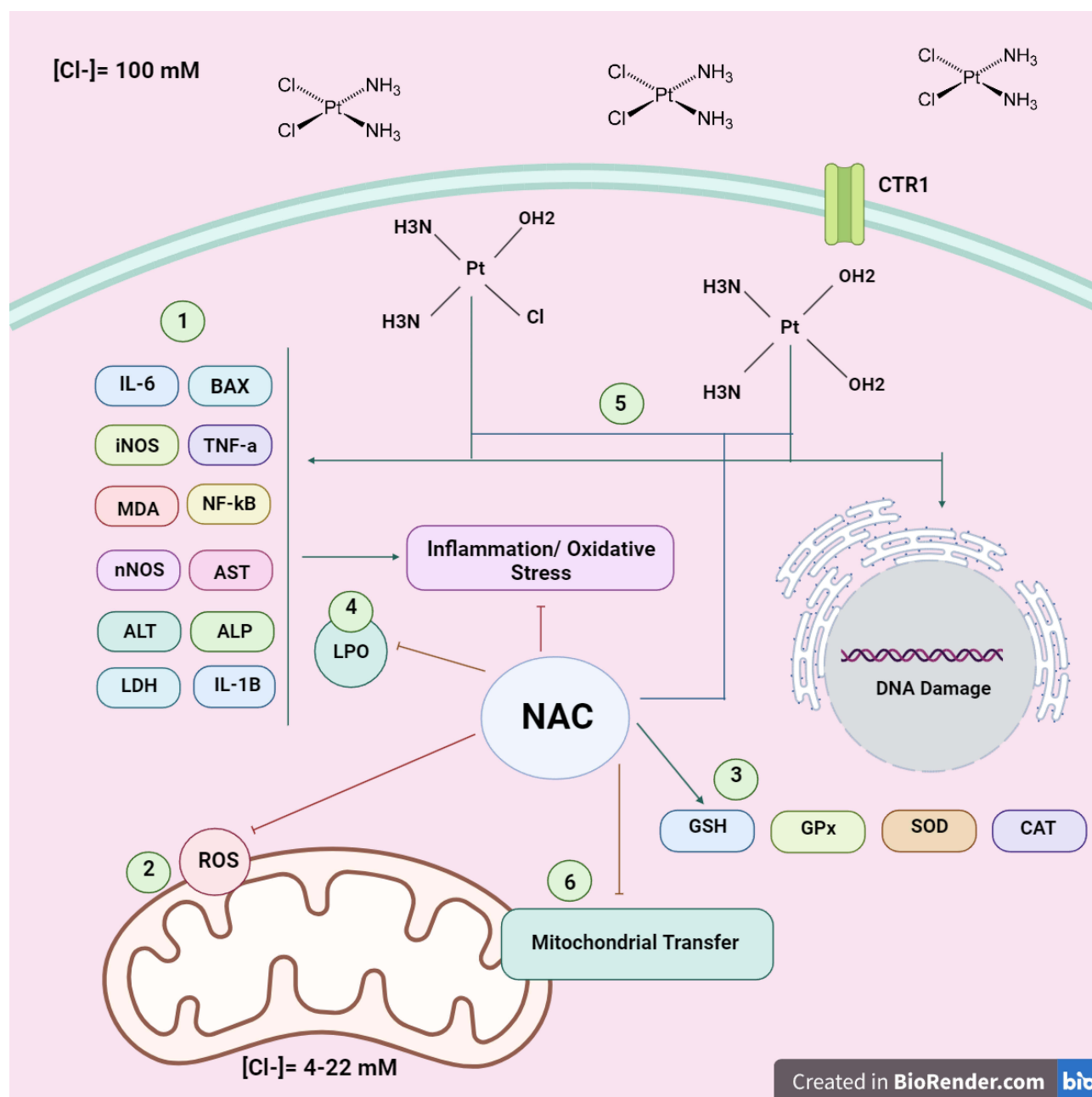


Figure 1 Hypothetical integrated molecular mechanisms of NAC action on cisplatin toxicity. (1). Reduction of inflammatory marker levels and oxidative stress. (2) Direct antioxidant activity of NAC against reactive oxygen species. Exocytosis and endocytosis processes and subsequently exert their action through various mechanisms. (3) Increase intracellular glutathione reserves and enhance detoxifying activity by antioxidant enzymes. (4) Inactivation of primary toxic products of lipoperoxidation. (5) Avidity of NAC by aqueous cisplatin species. (6) Inhibition of mitochondrial transfer.

Mitochondrial Transfer

Mitochondrial transfer involves introducing mitochondrial genes or the mitochondria into a host cell. This can result in major changes to the host's bioenergetic state and impact cell differentiation, inflammatory processes, cell survival, and drug resistance. Communication between the donor and recipient cells is essential for mitochondrial transfer, and it can be regulated by various structures, including extracellular vesicles (EV), tunneling nanotubes (TNT), and communicating junctions (GJ), among others.⁶¹

Mitochondria in neighboring cells can transfer to tumor cells, improving mitochondrial function and promoting tumor growth and metastasis.⁴⁷ In addition, considering several studies,^{61–65} correlate mitochondrial transfer with chemoresistance and with the recovery of cancer cells after treatment.

N-acetylcysteine has been found to inhibit mitochondrial transfer from stromal cells to cancer cells.^{47,64,66,67} however, the precise mechanism by which NAC carries out this action has not yet been determined. As a result, the attenuation of mitochondrial transfer has only been attributed to scavenging ROS.⁴⁷

NAC in Cancer

There is controversy surrounding the involvement of antioxidants and ROS in cancer.⁶⁸ Epidemiological studies on synthetic antioxidant supplementation are inconclusive and contradictory due to the antioxidant versus prooxidative properties of antioxidants and the involvement of antioxidants in intracellular signaling and redox regulation, which modulate proliferation, apoptosis, and gene expression.⁶⁹

NAC is a widely used antioxidant with therapeutic potential. NAC has been reported to have therapeutic benefits in various types of cancer: Kwon Y. J. reports that triple-negative breast cancer (TNBC) generates high levels of ROS and depends on ROS signaling to survive and progress malignantly by affecting the interaction between cancer cells and the tissue microenvironment (TME). However, NAC treatment can effectively decrease ROS production and ROS-mediated signaling, hindering cell survival, metastasis, and drug resistance in TNBC cells.⁴⁸

Monti et al suggested that NAC alone may inhibit breast cancer cell growth.⁷⁰

Amini et al propose enhancing the chemotherapeutic index for peritoneal surface malignancies of gastrointestinal origin with bromelain, N-acetylcysteine, and chemotherapeutic agents.⁷¹

According to Fen et al, low concentrations of NAC suppress pancreatic stellate cell (PSCs) activation and reduce oxidative stress, resulting in a quiescent state, inhibiting PSC viability, invasiveness, and migration, attenuating cancer-stromal interactions.⁷²

Jurkowska et al analyzed the effect of NAC on the proliferation of human neuroblastoma SH-SY5Y cells; the addition of NAC to the medium at non-cytotoxic concentrations resulted in the inhibition of SH-SY5Y cell proliferation after 48 h of culture ($P < 0.05$), increased in 3-mercapto pyruvate sulfurtransferase (MPST) activity, and, intracellular level of sulfur sulfane in these cells.⁷³

In an endogenous mouse model of malignant melanoma, human malignant melanoma cells' migration and invasive properties increased with the combination of NAC and the soluble vitamin E analog Trolox.⁷⁴ Similarly, N-acetylcysteine and vitamin E accelerated lung cancer progression in mice by reducing survival and increasing tumor progression by disrupting the ROS-p53 axis.⁷⁵

NAC in Protection Against Adverse Events During Cisplatin Chemotherapy in Experimental Animal Models and Humans Nephrotoxicity

As shown in Table 1, NAC has been shown to have a nephroprotective effect in different in vivo studies when used as a concomitant treatment after receiving cisplatin therapy, acting as a chemoprotective, without affecting the antitumor efficacy of platinum, decreasing significantly ($p = 0.001$) the levels of BUN, and creatinine, achieving significant improvement ($p = 0.001$) in results of histological studies of hemorrhage, necrosis and damage to tubule cells, significantly improving ($p \leq 0.05$) stress markers nephritic oxidative and inflammation, reducing LPO levels, and significantly ($p < 0.05$) increasing total antioxidant capacity (TAC) and enzymatic antioxidant activity^{28,54,76–79}

Ototoxicity

Table 2, shows in vivo studies and clinical trials set out in NAC show a potential otoprotective effect against ototoxicity caused by platinum, administered four h after CP without altering otoacoustic emissions (OAE) or auditory brainstem responses (ABR) and avoiding negative histopathological findings ($p < 0.05$). Since no significant changes in auditory

Table I Evidence of NAC in Protection Against Adverse Events During Cisplatin Chemotherapy in Experimental Animal Models

Study Model	NAC Beneficial Effect	Mechanism	References
Rats	Administering NAC after PC therapy improved renal markers such as creatinine, urea, and uric acid; compared to the group treated with PC alone, urinary glucose and protein excretion levels were significantly reduced. There was a significant reduction in LPO levels and a significant increase in serum TAC and enzymatic antioxidant activity.	The exact molecular mechanism is unknown, but NAC mimics the effect of antioxidants. Further studies are needed to know the molecular mechanism for the nephroprotective effect.	[54]
Rats	NAC inhibits cisplatin cytotoxicity and lipid peroxidation. NAC reduces cisplatin cytotoxicity and transforms necrosis into apoptosis. NAC also efficiently inhibited H ₂ O ₂ content.	NAC is an antioxidant independent, specific for the cisplatin mechanism, for its capacity to quench cisplatin reactivity inside the cells.	[28]
Rats	Neuroblastoma: VT significantly decreased in patients treated with NAC delayed four hours, with respect to the untreated control group, without affecting the antitumor efficacy of CP. Medulloblastoma: Delayed NAC did not significantly alter the efficacy of CP. Nephroprotection: NAC decreased PC-induced elevations in BUN.	Agents with reactive sulfhydryl groups will scavenge ROS and decrease oxidative stress, thus protecting cells and tissues from the toxic side effects of cisplatin chemotherapy.	[76]
Rats	BUN and Creatinine levels: There was a significant decrease in the CP+NAC group compared to the CP group. Histological study significantly improved hemorrhage, necrosis, and tubule cell damage in the CP+NAC group compared to the CP group.	NAC can reduce the disulfide bridges in proteins as a free radical capturer and produce metal chelation. Also has anti-inflammatory and antiapoptotic properties.	[77]
Rats	Treatment with NAC after CP administration significantly improved markers of nephritic oxidative stress and CP-induced nephritic inflammation compared to the group treated with CP alone. Significant increase in TAC in both serum and renal tissues.	NAC is a powerful antioxidant that reduces the reactive oxygen species, which have been proposed to be involved in cisplatin's genotoxic and cytotoxic action. NAC prevents the NF- κ B translocation into the nucleus, TNF- α mRNA increment in the kidney, and tissue apoptosis.	[78]
Rats	Treatment with PC performed three days after pretreatment with NAC revealed that blood urea nitrogen and creatinine levels were significantly reduced. The NAC pre-treated group before PC treatment showed significantly milder histopathological renal damage compared to the PC-treated group.	NAC is a thiol-containing antioxidant, which hinders cisplatin from removing glutathione or accumulating the peroxide, reducing the reactive oxygen species. It can protect the kidney by inhibiting the C5a-C5aR pathway and the downstream inflammatory reaction.	[79]
Rats	NAC evidenced signs of protection against cisplatin ototoxicity on the 7th day after application. NAC administered four hours after cisplatin injection prevented negative histopathological findings and attenuation of DPOAE and ABR thresholds caused by cisplatin.	NAC decreases hydrogen peroxide and increases glutathione synthesis. It might exert osteogenic activity via increased glutathione synthesis.	[80]
Guinea pigs	The group receiving 2% NAC showed significant otoprotection compared to the rest of the groups and the control group. Otoprotection was observed at all frequencies tested (1k, 2k, 4k, and 8k Hz).	The high concentration of NAC or the ototoxicity of adjuvants may induce the observed ABR threshold shift due to inflammation or ototoxicity.	[81]
Guinea pigs	Intraperitoneal administration of LN-acetylcysteine before cisplatin resulted in less hearing loss and a higher GSH/GSSG ratio than the trans tympanic formulations.	NAC is an antioxidant agent. Its low molecular weight allows it to permeate the round window.	[82]

(Continued)

Table 1 (Continued).

Study Model	NAC Beneficial Effect	Mechanism	References
Rats	In the group treated with CP+ NAC, fewer structural alterations in myelin and axoplasm were observed. A thin and loose myelin sheath was found, suggesting remyelination. The intensity of BAX, iNOS, and TNF- α immunoreactivity decreased. MDA and NF- κ B levels were significantly lower than those of the CP-treated group, SOD and GSH levels were significantly higher than those of the CP-only treated group. Number of axons is equal to the control group.	The main action of the NAC was through the elevation of the glutathione (GSH). NAC is a precursor for GSH and aids in its synthesis.	[83]
Rats	NAC significantly attenuated CP-induced changes in brain cholinergic function. It improved brain oxidative/antioxidant status, increasing GSH levels and the activities of GPx, GST, SOD, and CAT. Reversed the overproduction of proinflammatory cytokines in the brain and serum.	NAC possesses neurovascular protective mechanisms, like downregulating inflammation and oxidative stress, and also can cross the blood-brain barrier and increase the level of brain-derived neurotrophic factors.	[84]
Rats	NAC supplementation and cisplatin administration reversed the prooxidant and proapoptotic effects of cisplatin. Antioxidant supplementation with NAC was able to attenuate cisplatin-induced anxiety.	NAC mitigates cisplatin-induced inhibition of dendritic branching, oxidative stress, and apoptosis of the cells in the hippocampus.	[85]
Rats	Cardiac Markers: NAC supplementation after cisplatin therapy reduced CK-MB, LDH, CMLC-I, cTnI, TOC, and ROOH, compared to the cisplatin alone group. CT levels were increased. Histopathology: Interstitial edema and mild vacuolization, lower than that observed in the CP group. Improvement of hemorrhage.	The beneficial effects of NAC are associated with its antioxidant and anti-inflammatory properties.	[86]
Rats	Coadministration of NAC attenuated cisplatin-induced changes in oxidative stress and cardiodynamic parameters, as well as morphological changes in the myocardium and coronary vasculature.	NAC contains a sulfhydryl group that may contribute to long-term antioxidant protection; its antioxidant properties decrease reactive oxygen species.	[87]
Rats	Decrease in AST and ALT enzyme activities in NAC + CP Group compared to Control and CP groups. NAC administration reduced CP-induced inflammation by increasing the level of NF- κ B and decreased oxidative stress caused by CP by decreasing the level of GPx. Histopathological analyses showed that NAC improved liver morphology. NAC promoted Bcl-2 signaling and decreased p53 signaling.	NAC exhibits direct antioxidant activity against cells. It also suppresses cytokine expression and has an anti-inflammatory property by inhibiting the expression of NF- κ B.	[88]
Rats	AST, ALT, and ALP activities were significantly reduced in the NAC + CP group compared to the CP group. NAC+CP treatment attenuated the effects of CP on liver tissue MDA, CAT, SOD, and GSH and remarkably restored the usual liver architecture.	NAC inhibits lipid peroxidation and scavenging radical oxygen species. Is capable of restoring the pro-oxidant /antioxidant balance.	[89]

Abbreviations: NAC, N-acetyl cysteine; CP, Cisplatin; LPO, Lipid Peroxidation; TAC, Total Antioxidant Capacity; H₂O₂, Hydrogen Peroxide; VT, Tumor Volume; BUN, Blood urea nitrogen; DPOAE, distortion product otoacoustic emission responses; ABR, auditory brainstem response; GSH, Glutathione; GSH/ GSSG, reduced/oxidized glutathione ratio; Oxidative/antioxidant markers: MDA, malondialdehyde; SOD, superoxide dismutase; neurotoxic/neuroprotective markers; iNOS, Inducible nitric oxide synthase; nNOS, neuronal nitric oxide synthase inflammatory mediators; TNF- α , tumor necrosis factor-alpha; NF- κ B, nuclear factor κ B; GPx, Glutathione peroxidase; CK-MB, MB isoenzyme of creatine kinase; LDH, lactate dehydrogenase; CMLC-I, Cardiac Myosin Light Chains I; cTnI, cardiac troponin T; TOC, total oxidizing capacity; ROOH, lipid hydroperoxide; Bcl-2, B-cell lymphoma 2; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase.

Table 2 Evidence of NAC in Protection Against Adverse Events During Cisplatin Chemotherapy in Humans

Study Model	Results	Mechanism	References
Children	There were no significant changes in hearing thresholds in ears treated with N-acetylcysteine.	NAC analogs of cysteine may protect the inner ear due to their potent antioxidant activity and ability to synthesize glutathione.	[90]
Patients treated with cisplatin.	In treated ears, no significant changes in auditory thresholds were recorded. In control ears, cisplatin-induced a significant decrease in hearing thresholds in the 8000 Hz frequency band.	Due to its action mechanism as an antioxidant, N-acetylcysteine may also possess anti-inflammatory properties.	[91]
Children and adolescents	Compared to the control group, NAC decreased the likelihood of cisplatin-induced hearing loss (CIHL) at the end of treatment. NAC increased glutathione.	NAC can restore GSH synthesis and intrinsic antioxidant capacity, counteracting cisplatin-induced effects on the cochlea.	[92]

thresholds were recorded in the NAC-treated groups (T9,10) a higher reduced/oxidized glutathione ratio GSH/GSSG was observed compared to the other groups $p \leq 0.001$.^{80–82,90–92}

In animal models, NAC is usually administered through intratympanic administration. This route is ideal as it does not interfere with the antineoplastic ability of cisplatin, and it effectively delivers the drug to the inner ear in concentrated amounts.^{81,91,93}

Neurotoxicity

For neurotoxicity assessment, the studies in [Table 1](#) evaluated the effect of NAC concomitant to PC therapy, showing improved oxidant/antioxidant status; fewer structural alterations were found in myelin and axoplasm. GSH, SOD levels, and GPx, GST, SOD, and CAT activities were increased. Reversing proinflammatory cytokines, prooxidant, and proapoptotic effects of cisplatin. Decreasing levels of BAX, Inducible nitric oxide synthase (iNOS), tumor necrosis factor- α (TNF- α), malondialdehyde (MDA), and nuclear factor κ B (NF- κ B) ($p < 0.05$).^{83–85}

Other Toxicities

In the evaluation of other toxicities, such as cardiotoxicity, as shown in [Table 1](#), late or concomitant administration of NAC to cisplatin therapy has shown a reduction in oxidative stress and cardio dynamic stress parameters, decreasing levels of MB isoenzyme of creatine kinase (CK-MB), lactate dehydrogenase (LDH), Cardiac Myosin Light Chains 1 (CMLC-1), cardiac troponin T (cTnl), total oxidizing capacity (TOC), lipid hydroperoxide (ROOH), increasing levels of TAC, and showing a milder degree of interstitial oedema, vacuolization and improvement of hemorrhage.^{86,87}

In the case of hepatotoxicity, [Table 1](#). We found decreased aspartate aminotransferase (AST) and alanine aminotransferase (ALT) enzyme activities. NAC promoted B-cell lymphoma 2 (Bcl-2) signaling and decreased p53 signaling. NAC+CP treatment attenuated the effects of CP on MDA in liver tissue, CAT, SOD, and GSH.^{88,89}

Administering NAC after cisplatin treatment can provide delayed chemoprotection. This is because it helps maintain cisplatin's early DNA alkylation mechanism in rapidly dividing cancer cells while also providing antioxidant protection against ROS, likely the main cause of toxicity in differentiated cells.⁷⁶

Conclusion

The evidence in the literature displayed in the current review indicates that the NAC administration can be a promising approach to address some current issues related to cisplatin and other conditions. NAC can improve the intracellular cysteine pool, enhance GSH synthesis, and boost endogenous antioxidant capacity through different enzymes. These findings indicate that NAC administration is a potential candidate for chemoprotection due to its ability to react with ROS, which can decrease side effects and improve both patient treatment and long-term outcomes.

Further human clinical studies are urgently needed as most studies have only been reported in animal models. Hence, it is necessary to define the effective dose and the optimal route of administration for better chemoprotection. This could aid in developing personalized therapies, reducing toxicity and complications associated with treatments. As a result, it would lower the costs of medical care and improve the quality of life of patients receiving chemotherapy.

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