

N-Acetylcysteine Role in Maintaining Renal Function in Cancer Patients with Cisplatin-Based Chemotherapy

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Background: Cisplatin is a cornerstone chemotherapeutic agent used widely to treat various solid malignancies. Despite its efficacy, the usage of cisplatin is limited by its dose-dependent nephrotoxicity causing cisplatin-induced acute kidney injury (AKI) in up to 45% of treated patients. Current preventive strategies are limited to supportive measurement resulting in questionable clinical outcomes. N-acetylcysteine (NAC), a thiol-containing compound with antioxidant and anti-inflammatory properties, is already known for its safety.

Purpose: This review aims to explore the mechanisms of cisplatin-induced AKI, the role of NAC in its prevention, and the current evidence.

Methods: A narrative review has been conducted of several literature, including preclinical and clinical studies evaluating NAC's efficacy in preventing cisplatin-induced AKI.

Results: Cisplatin has cytotoxic effect via DNA structures disruption, leading to impairment of cell repair mechanism, triggering apoptosis that works effectively against cancer cells. However, cisplatin also accumulates in renal proximal tubular epithelial cells, disrupting DNA structures, increasing reactive oxygen species (ROS), inducing mitochondrial dysfunction and inflammation, all leading to apoptosis. NAC can counteract these mechanisms by scavenging ROS directly via its thiol group and indirectly by replenishing glutathione. Preclinical studies have demonstrated consistent NAC nephroprotective effects. However, findings from clinical studies remain inconsistent due to limited sample sizes, varied dosing regimens, and differences in administration routes, making comparison between studies difficult to conduct.

Conclusion: NAC exhibits strong nephroprotective properties through antioxidant, anti-inflammatory, and cytoprotective mechanisms as consistently shown in preclinical studies. Despite the limited current clinical evidence supporting these findings, NAC remains a promising agent for cisplatin-induced AKI prevention. Future research should focus on large-scale, well-designed, standardized clinical trials with optimized dosing strategies to validate NAC's efficacy and establish its clinical role.

Keywords: cisplatin, acute kidney injury, N-acetylcysteine, nephroprotective

Introduction

Cancer is one of the most significant global health challenges, with a profoundly unequal burden that affects populations worldwide.^{1,2} Globally, cancer has caused the death of 9.6 million lives and affected 18.1 million people in 2018. Alarming, over 70% of these cases occurred in low- and middle-income countries, with incidence rates expected to nearly triple in these regions by 2040. According to Baseline Health Research (BHR) data, Indonesia experienced a rise



in cancer prevalence from 1.4% in 2013 to 1.49% in 2018.² This growing burden highlights the urgent need for equitable cancer care solutions worldwide.

Cancer treatments vary depending on the disease type and stage. There are several approaches, for example, surgery, radiation therapy, chemotherapy, and other advanced modalities. Surgery remains the option for localized tumors, radiation therapy employs high doses of radiation to eliminate cancerous cells, and chemotherapy is a systemic and effective treatment using cytotoxic agents. Cisplatin is one of the most potent agents and a pioneering metal-based chemotherapy drug. Cisplatin-based chemotherapy continues to be widely used for treating various solid malignancies.¹ However, cisplatin is known for its nephrotoxicity, causing around 5–45% acute kidney injury (AKI) in patients with malignancies.^{3–9} Cisplatin nephrotoxicity has a high clinical burden, developing in about a third of all treated cases.¹⁰

Despite its toxicity, cisplatin remains widely used because no alternative matches its efficacy.⁸ Recently, management of cisplatin-induced AKI relies on supportive measurements, such as hydration, electrolyte supplementation, diuresis, and minimizing exposure to additional nephrotoxic agents. No practical guideline currently exists for the treatment and prevention of cisplatin-induced AKI in patients with malignancies.¹¹ Previous studies reported mannitol and furosemide usage as diuretic agents and additional magnesium supplementation to reduce cisplatin nephrotoxicity. Nevertheless, the available data shows contradicting conclusions, primarily based on small studies, and do not include the Indonesian population. Therefore, further studies on cisplatin-induced AKI prevention and management are needed.^{11–15}

N-acetylcysteine (NAC) has long been used in clinical practice beyond oncology-related research. For instance, NAC has been the standard antidote for Acetaminophen overdose because of its ability to prevent liver injury by rapidly restoring hepatic glutathione and neutralizing toxic metabolites.^{16,17} Moreover, NAC has also been evaluated in the nephrology setting for prevention of contrast-induced nephropathy. Despite the heterogeneous findings, some studies suggest that NAC shows a modest protective effect from contrast-induced nephropathy.¹⁷ These established uses emphasize NAC's translational potential as a nephroprotective agent, proposing a convincing rationale for further exploration in its promising role in preventing cisplatin-induced acute kidney injury (AKI).

As a widely used mucolytic drug, NAC has been known for its antioxidant properties and a good safety profile. The mechanism of cisplatin nephrotoxicity is through tubular renal cell apoptosis by generating reactive oxygen species (ROS), causing mitochondrial dysfunction, lipid peroxidation, DNA strand damage, inflammation, and renal vascular impairment. The NAC regulates glutathione (GSH) inside the cell to inhibit lipid peroxidation and ROS production, potentially preventing cisplatin-induced nephrotoxicity.^{18,19}

A number of other antioxidants and cytoprotective compounds such as curcumin, taurine, and vitamin E have also been proposed for its nephroprotective features. However, NAC stands out among these compounds for several reasons. First, unlike other compounds, NAC is already used in clinical practice at known doses and with a well-characterised safety profile. Second, its mechanisms directly align with the primary pathways of cisplatin nephrotoxicity. Third, NAC is widely available and cost-effective unlike many experimental agents. These qualities make NAC a particularly compelling candidate for translation from bench to bedside in oncology-associated renal toxicity.^{20–25}

Several ongoing studies have focused on proving NAC efficacy in preventing cisplatin-induced nephrotoxicity.^{26–31} Serum creatinine is the common biomarker for evaluating renal function. However, it is not the most sensitive and specific biomarker in detecting cisplatin-induced nephrotoxicity. Several biomarkers have been proposed to have better performance in quickly detecting renal function declines indicating cisplatin-induced nephrotoxicity, such as Kidney Injury Molecule-1 (KIM-1), Neutrophil Gelatinase-Associated Lipocalin (NGAL), and Interleukin 18 (IL-18).^{32–36}

Nevertheless, a key translational gap remains between robust preclinical evidence and the evidence from human studies. Preclinical models consistently show that cisplatin triggers reactive oxygen species (ROS) accumulation, mitochondrial dysfunction, inflammation and apoptosis in renal tubular cells, and that NAC can alleviate these changes.^{27,37} In contrast, clinical trials of NAC in cisplatin-induced AKI prevention have been limited in number, varied in design, doses, routes, timing, and frequently underpowered or inconsistent in outcome definitions. This discrepancy highlights the need for standardized clinical trials of NAC in this context and supports the rationale for the present review.

This review aims to summarize the current evidence regarding the efficacy of NAC in preserving renal function and preventing cisplatin-induced AKI in patients undergoing chemotherapy. In addition, this review also explores the

potential use of novel biomarkers beyond serum creatinine, which may provide earlier and more sensitive detection of renal function decline in the context of cisplatin-induced nephrotoxicity. The clinical implications of this review are significant for determining the optimal use of NAC in clinical practice.

Methods

The narrative review is conducted to summarize recent evidence on the protective role of N-acetylcysteine (NAC) against cisplatin-induced acute kidney injury (AKI). Literature searching was performed in several databases including but not limited to Pubmed, Scopus, and Google Scholar using several keywords such as “N-acetylcysteine”, “cisplatin”, “acute kidney injury”, “nephrotoxicity”, and “renal protection”. We included relevant articles published in English with available full text up to July 2025. Additional sources were identified through reference lists of relevant publications and manual searching when necessary. We reviewed both experimental and clinical studies to understand the mechanism of NAC in preventing cisplatin-induced nephrotoxicity. We excluded irrelevant studies unrelated to cisplatin or renal outcomes. We summarized the findings descriptively, mainly focusing on cisplatin nephrotoxicity mechanisms, NAC’s mechanisms of action in countering the cisplatin nephrotoxicity, and the evidence of potential clinical applications.

Cisplatin-Induced Nephrotoxicity

Cisplatin (cis-diamminedichloroplatinum(II)) is a widely used chemotherapeutic agent for treating various solid-organ cancers, including head and neck, lung, testis, ovary, and bladder cancer. Despite its clinical efficacy, cisplatin has significant nephrotoxicity effects. The renal manifestations of cisplatin are diverse. Among the manifestations, AKI is the most frequent and clinically significant manifestation (20–30% of patients). The drug’s nephrotoxic effects cause other renal manifestations such as severe hypomagnesemia, Fanconi-like syndrome, distal renal tubular acidosis, hypocalcemia, renal salt wasting, impaired urine concentrating ability, hyperuricemia, transient proteinuria, erythropoietin deficiency, and thrombotic microangiopathy. Although cisplatin’s nephrotoxic effects have been recognized for decades, it is continued to be used in current treatment regimens supported by its generic availability and ongoing clinical trials.⁸

In 1965, Barnett Rosenberg discovered a platinum-based heavy metal complex that can inhibit cell division without affecting cell growth. That chemical complex is cis-diamminedichloroplatinum(II) and is widely known as cisplatin. Animal studies have reported cisplatin’s superior efficacy compared to other platinum complexes in treating malignancies, leading to its clinical adoption. In 1978, the Food and Drug Administration (FDA) officially approved the clinical usage of cisplatin.³⁸ Within 24 hours after cisplatin administration through intravenous injection, approximately 65–95% of cisplatin in the bloodstream binds to plasma proteins such as albumin, transferrin, and cysteine.³⁹ This plasma protein binding will deactivate the drug partially.^{38,39} Cisplatin primarily uses passive diffusion across the plasma membrane to enter cancer cells.³⁸ Once inside the cell, water molecules replace the chloride ligands in the low-chloride intracellular environment, transforming cisplatin into a positively charged, highly reactive species.³⁸ This activated cisplatin forms covalent bonds with nucleophilic sites in DNA, particularly the nitrogen atoms of purine bases, disrupting the DNA structure by inducing intra- and inter-DNA crosslinks, thereby interrupting DNA replication and transcription.^{1,40} The Cellular repair mechanism activates when a cell detects the resulting DNA damage. However, if this mechanism fails, the cell will undergo apoptosis, a programmed cell death. This potent cytotoxic effect of cisplatin works well against malignant cells, attacking the cells and shrinking the tumor.^{1,40}

Despite its effect on fighting cancer cells, cisplatin’s cytotoxic properties also affect other cells in the human body, including renal cells, causing cisplatin-induced AKI. Cisplatin-induced nephrotoxicity involves several interrelated mechanisms primarily associated with the overproduction of ROS. Cisplatin induces mitochondrial dysfunction and decreases antioxidant enzymes such as GSH, catalase (CAT), and superoxide dismutase (SOD) upon its accumulation in renal tubular epithelial cells. The high amount of ROS will cause oxidative stress and endoplasmic reticulum (ER) stress. Necrosis and apoptosis of the renal tubular cells can be triggered by oxidative damage, resulting in kidney tissue injury. Moreover, accumulation of ROS can cause renal ischemia by inducing vasoconstriction of the microvasculature. The accumulation of cisplatin also promotes pro-inflammatory cytokines and chemokines production, ultimately decreasing the glomerular filtration rate, leading to AKI.⁴¹

The cisplatin accumulation at concentrations up to five times higher than plasma levels in the proximal tubular cells mainly affects the most susceptible S3 segment. Organic cation transporter 2 (OCT2) and copper transporter (Ctr1) mediate cisplatin uptakes, making patients with OCT2 overexpression have a higher risk of cisplatin-induced nephrotoxicity. Meanwhile, multidrug and toxin extrusion transporter 1 (MATE1) enhances cisplatin excretion into the urine, offering protection from its nephrotoxicity.⁷ As cisplatin binds to GSH, ROS will be generated, attacking polyunsaturated fatty acids (PUFAs), causing lipid peroxidation. This process produces toxic byproducts such as malondialdehyde (MDA) that induce mitochondrial dysfunction, ER stress, apoptosis, and inflammation.⁴¹ Cisplatin induces apoptosis through several pathways. First, the intrinsic pathway is mitochondrial apoptosis through caspase-2 activation via the release of cytochrome c and apoptosis-inducing factor (AIF) following BAX translocation. The p53 protein especially plays a role in disrupting the mitochondrial membrane when it senses DNA damage. Second, the extrinsic pathway is a death signal from inside the cell through caspase-8 activation via TNF receptor binding. Lastly, the ER stress pathway induces caspase-12 activation, leading to apoptosis.^{7,41}

Inflammation also has a significant contribution in worsening renal cell injury through activation of pathways such as NF- κ B by the infiltration of immune cells (CD4⁺ T cells, macrophages, neutrophils, mast cells) and the massive production of proinflammatory cytokines (TNF- α , IL-6, IL-33, CXCL1, CXCL2, CXCL16). Hypoxia and tubular injury are further intensified by vascular dysfunction through AT1 receptor-mediated vasoconstriction, decreasing renal blood flow.^{7,41} Finally, mitochondrial DNA crosslinking is the primary mechanism in cisplatin-induced DNA damage. Therefore, proximal tubules cell that contains a high amount of mitochondria are especially vulnerable to injury.⁴² Figure 1 (Subfigure 1A) further illustrates the nephrotoxic mechanism of cisplatin.

Higher doses, frequencies, and cumulative exposure increase the risk of cisplatin-induced nephrotoxicity. The risk is especially higher in certain vulnerable populations such as the elderly, females, smokers, and patients with hypoalbuminemia and pre-existing renal insufficiency. Acute kidney injury (AKI) is the primary clinical manifestation, occurring in approximately 20–30% of patients. Non-oliguric AKI typically appears a few days after cisplatin administration, marked by increased serum creatinine and blood urea nitrogen levels. Small amounts of urinary glucose and protein might be detected indicating proximal tubular dysfunction.⁸ The common complication that can occur after repeated cisplatin doses, even without a decreased glomerular filtration rate (GFR), is hypomagnesemia. The recovery of renal function usually begins in 2–4 weeks after cisplatin administration. However, older patients and those receiving consecutive cisplatin cycles might also develop progressive and permanent nephrotoxicity despite preventive measures. Other clinical manifestations in cisplatin-induced nephrotoxicity include Fanconi-like syndrome, renal tubular acidosis, hypocalcemia, renal salt wasting, impaired renal concentrating ability, hyperuricemia, transient proteinuria, erythropoietin deficiency, thrombotic microangiopathy, and chronic kidney disease (CKD).⁸

The focus of cisplatin-induced nephrotoxicity management is limiting exposure while maintaining therapeutic benefit by reducing the dose, switching to less nephrotoxic agents like carboplatin or oxaliplatin, and avoiding additional nephrotoxic drugs like NSAIDs. The preventive strategies involve adequate hydration, diuretic usage, and magnesium supplementation.¹¹ Giving saline hydration in short duration (2–6 hours) and low volume (2–4L) has been reported to be well tolerated and effective in reducing nephrotoxicity.^{11,42} Enhancing cisplatin clearance by administering diuretics like mannitol and furosemide also has evidence of reduced nephrotoxicity risk.^{11,43} However, this effect is not found to be significant in the elderly. Adding Magnesium supplementation to cisplatin-induced nephrotoxicity preventive measures might be beneficial since the evidence consistently shows its protective effects by preventing hypomagnesemia-induced OCT2 upregulation and oxidative stress.¹¹

One cohort published in 2023 reported that among 109 head and neck cancer patients treated with high-dose cisplatin, the incidence of AKI was 12.8%. Half of the patients with cisplatin-induced AKI were stage 1 based on KDIGO criteria. However, the incidence of discontinuation of cisplatin chemotherapy regarding severe cisplatin-induced AKI was low, with only one patient reported.⁴⁴ Recent studies, however, have been reported higher incidences of cisplatin-induced AKI, ranging from 53.9% to 69%, but the majority of cases still categorized as stage 1 AKI.⁴⁵

Biomarker for Cisplatin-Induced AKI

In order to prevent progression to irreversible renal damage, early detection of AKI is essential. Based on KDIGO criteria, diagnosis of AKI can be established when there is an increase of serum creatinine (SCr) ≥ 0.3 mg/dL within 48 hours, ≥ 1.5 times from baseline within 7 days, or urine output drops below 0.5 mL/kg/hour for 6 hours.⁴⁶ Urine output, SCr, and blood urea nitrogen (BUN) are the standard and widely used tools in detecting renal function declines. However, these methods have limitations in detecting early AKI. Elevation of SCr typically occurs 48–72 hours after the renal damage and is highly affected by several factors such as muscle mass, sex, age, and hydration status.^{35,47} Therefore, recent studies have been focusing on finding novel biomarkers that can respond earlier to detect renal injury and more reliable than the traditional markers. These new biomarkers potentially provide a more rapid and sensitive diagnostic to cisplatin-induced AKI.^{33,34} Moreover, some of these biomarkers might be able to differentiate glomerular versus tubular injury, giving more insights into the underlying mechanism and possibly directing a more precise treatment approach.

Kidney injury molecule-1 (KIM-1) is a transmembrane glycoprotein in the epithelial cells of the proximal tubule that is only expressed extensively after injury. Normal and healthy kidney cells are not supposed to have this protein. Therefore, the finding of this protein in the urine serves as a sensitive indicator in apoptosis and tubular damage.⁴⁸ The level of KIM-1 can be detected as early as 24 hours post-injury. The level steadily increases up to sixfold by day 7 following cisplatin administration, serving this biomarker as a possible indicator for cisplatin-induced AKI.^{33,34} Previous studies reported that there is a significant elevation of KIM-1 urinary level in lung cancer patients that received cisplatin-based chemotherapy.³² The area under the receiver operating characteristic curve (AUC-ROC) for AKI prediction using KIM-1 reaches 0.858 and as high as 0.94 on day 3 post-cisplatin when AKI is defined as a 1.5-fold increase in SCr.^{32,36,49} The typical procedure to measure KIM-1 levels in the urine is enzyme-linked immunosorbent assay (ELISA). The alteration in urinary pH might affect the concentration of KIM-1, giving a false interpretation.⁵⁰

In response to nephrotoxic or ischemic insults, proximal tubular cells rapidly secrete neutrophil gelatinase-associated lipocalin (NGAL).⁴³ This biomarker rises 2–3 hours after cisplatin administration and reaches the maximum concentration within 12–24 hours.^{33,34} The levels of urinary NGAL increase significantly by day 2 post-cisplatin administration, predicting AKI with an AUC-ROC of 0.87.^{34,49} ELISA method is used to quantify NGAL level. While serving as a promising biomarker for its sensitivity, the specificity of NGAL is limited. Systemic inflammation and systemic stress such as sepsis can elevate NGAL level.^{33,34}

Under oxidative stress, proximal tubular cells release L-type fatty binding protein (L-FABP) as early as 6 hours following injury. It is measurable via ELISA and is a powerful and sensitive indicator for cisplatin-induced AKI, with an AUC-ROC of 0.977 for a 10.28-fold L-FABP increase from baseline.⁵¹

Following an ischemic or toxic injury in the proximal tubule, the epithelial cells release a pro-inflammatory cytokine named Interleukin-18 (IL-18). The IL-18 levels rise within 1–2 days before there is a noticeable increase in SCr level, making it a possible biomarker for detecting early inflammation-mediated AKI. Measurement is commonly done by using ELISA methods. However, just like NGAL, the level is affected by other inflammatory conditions in the body; interpreting only based on laboratory data is unreliable.⁴⁸

Damaged tubular epithelial cells release a lysosomal enzyme named N-acetyl- β -D-glucosaminidase (NAG). Based on studies on animals, NAG levels reach their peak around 3–5 days following cisplatin administration and normalize in 2–12 weeks. However, NAG levels do not consistently correlate with cisplatin dose nor reflect the extent of tubular injury, limiting its predictive power.^{49,52}

As a low-molecular-weight protein, β 2-microglobulin (β 2M) accumulates in urine following proximal tubule injury, making it a sensitive marker for both structural damage and functional impairment in kidney dysfunction.⁵³ Under physiological conditions, the kidneys catabolize the majority of β 2-microglobulin during normal protein turnover. Renal impairment leads to a 25–60 fold elevation in serum β 2M concentrations. In vitro study by Zhang et al⁵⁴ demonstrated that cisplatin rapidly interacts with β 2M at pH 7.0. The detection of a platinum(II)-bridged β 2-microglobulin dimer is significant because cisplatin's complexation with proteins is known to enhance β 2M's antigenicity. This interaction may also contribute to β 2M aggregation, which exacerbates its pathological effects eventually.⁵⁴

One of the essential components of the glomerular filtration barrier is podocytes. These podocytes contain nephrin as a protein component in their slit diaphragm. Glomerular injury can be detected by the presence of this protein in the urine in conjunction with the findings of other tubular injury markers. In animal models, nephrin levels in the urine increase significantly on days 3, 5, and 7 post-cisplatin injection. Meanwhile, its expression in kidney tissue decreased from day 3 post-cisplatin injection.⁵²

Albumin is a protein with a huge molecular size and usually should not be found in the urine. Albumin in the urine, or albuminuria, reflects both glomerular and tubular injury. Albuminuria levels reach their maximum concentration on days 4–10 post-cisplatin infusion and decline over 2 weeks. However, its early diagnostic accuracy is relatively low, with an AUC-ROC of 0.52 at 24 hours, and only slightly improved to 0.7 by day 4.⁴⁹

NAC as a Nephroprotective Agent

N-acetylcysteine (NAC) is an acetylated analog of the amino acid cysteine with the chemical formula of $C_5H_9NO_3S$.⁵⁵ As a precursor of GSH, cysteine serves as a key antioxidant responsible for maintaining redox balance in the body. Oxidative stress results from an imbalance between antioxidants and ROS and leads to cellular damage and dysfunction.⁵⁶ NAC structure constructed from a sulfhydryl (-SH) group, an acetyl group (-COCH₃), and an amine group (NH₂), making it possible to play a role as a nucleophile and a radical scavenger that donates electrons.^{55,56} NAC demonstrates antioxidant activities both from direct and indirect pathways. Directly, reactive oxygen and nitrogen species (RONS), such as hydroxyl radicals ($\bullet OH$), nitrogen dioxide ($\bullet NO_2$), carbon trioxide ($CO_3\bullet^-$), superoxide ($O_2\bullet^-$), hydrogen peroxide (H_2O_2), and peroxynitrite ($ONOO^-$) will react with its thiol group. Meanwhile, NAC also increases intracellular cysteine levels to promote GSH biosynthesis indirectly.^{55,56} Moreover, NAC is also known as a mucolytic drug because of its ability to alter the structural properties of mucus by cleaving disulfide bonds. NAC can reduce inflammatory cascades by downregulating pro-inflammatory cytokines such as TNF- α , IL-1 β , and IL-6 and suppressing NF- κB activation by inhibiting nuclear translocation.⁵⁵

Recent studies indicated that NAC could also minimize cisplatin toxicity after cisplatin-based chemotherapy. Cisplatin chemotherapy would worsen along with the higher doses usage. Cisplatin-induced nephrotoxicity is a serious and common adverse effect. It occurs in approximately 25–35% of adults and up to 70% of children undergoing treatment. Several factors contribute to this kidney damage, such as increased oxidative stress, mitochondrial dysfunction, inflammation, DNA damage, and the subsequent apoptosis. Cisplatin tends to build up in the kidney's proximal and distal tubules, leading to the death of epithelial cells and disrupting tubular reabsorption. This process activates the tubuloglomerular feedback system and, along with tubular blockage, results in reduced glomerular filtration.^{57–59}

The mechanisms of cisplatin-induced nephrotoxicity have similarities to contrast-induced nephropathy that involves oxidative stress and vasoconstriction.^{60–62} Cisplatin weakens antioxidant defenses by decreasing several substances, such as SOD and GSH, enhancing oxidative stress by elevating markers such as malondialdehyde (MDA). NAC encounters these conditions by scavenging ROS and restoring GSH levels, reducing lipid peroxidation and cellular injury. Additionally, p53 activation is inhibited by NAC, terminating cisplatin-induced apoptosis of renal tubular cells. Cellular metabolism and mitochondrial integrity are also protected by NAC's ROS-reducing properties.⁶³

Not only playing a role as an antioxidant, NAC also serves as an inflammatory modulator. Beyond oxidative stress, inflammatory cascades also contribute to damage to renal tissue during AKI. Previous studies have reported NAC's ability to inhibit chemotactic factors such as CXCL1, CXCL6, and MCP-1.²⁷ Inside the cell, cisplatin undergoes aquation, replacing its chloride ligands with water molecules, which then interact with nucleophilic DNA targets. NAC mitigates cisplatin-induced nephrotoxicity on a molecular level by binding its thiol group to reactive species reducing its interaction with cisplatin.⁶⁴ Further explanation of NAC mechanism of action as a nephroprotective agent illustrated on Figure 1 (Subfigure 1B).

Evidence from Preclinical and Clinical Studies

NAC's nephroprotection properties against cisplatin-induced AKI have been demonstrated in numerous preclinical and clinical studies (Table 1). A study by Kinbara et al⁶⁵ showed that prophylactic N-acetylcysteine administration significantly reduced serum $\beta 2$ -microglobulin levels. NAC nephroprotective effects may primarily stem from glomerular preservation.⁶⁵

Table I Summary of Preclinical and Clinical Studies on the Efficacy and Safety of NAC in Cisplatin-Induced Nephrotoxicity,^{26,27,30,31,66,67,68}

Study (Author, Year)	Study Type	Subjects	NAC Dose & Route	Main Findings	Notes
Preclinical Studies					
Abdel-Wahab et al 2017 ⁶⁶	Animal (rat)	Adult male albino rats	NAC 50mg/Kg, 3 days after cisplatin, 3 times weekly for 4 consecutive weeks	↓ MDA, urinary protein/glucose; ↑ antioxidant enzymes, ↑ TAC	Mechanistic pathways not explored; small sample size; limited to short-term rat model.
Gunturk et al 2019 ²⁶	Animal (rat)	Male Wistar albino rats	NAC 250mg/kg, IP, 3 consecutive days after cisplatin	↓ Creatinine, BUN; improved renal histology	Incomplete inflammation assessment; possible pro-inflammatory effect of high-dose NAC not evaluated.
Huang et al 2019 ²⁷	Animal (mouse)	C57BL/6 mice	NAC 50 mg/kg, IP, 3 consecutive days after cisplatin	↓ serum creatinine, BUN, KIM-1 urine, MDA, C5aR expression, neutrophil infiltration, inflammatory cytokines, ↑ antioxidant enzymes,	Lack of pharmacokinetic data, NAC tissue levels not measured; unclear if effects are direct or systemic.
Clinical Studies					
Visacri et al 2019 ⁶⁸	RCT (double-blind)	57 Head & neck cancer patients	NAC 600 mg/day PO, 7 consecutive days (2 days before chemotherapy, on the chemotherapy day, and 4 days after chemotherapy)	No improvement in renal or oxidative markers	Low-dose oral NAC with poor bioavailability; sample loss and assay variability limited oxidative stress analysis.
Ibraheem et al ^{30,31}	RCT (open-label)	52 Cisplatin-treated cancer patients	NAC 2 × 600 mg 4 doses in 24 hours before chemotherapy	Results have not been reported	Results have not been reported
Azam et al 2024 ⁶⁷	RCT (open-label)	70 female patients with non-haematological malignancies	NAC 1200 mg PO, 7 consecutive days (1 day before chemotherapy, on the chemotherapy day, and 5 days after chemotherapy). Repeated for 4 consecutive cycles	Slight improvement in renal function biomarkers, but not statistically significant	Female-only sample, lack of placebo control and blinding, limited biomarkers (only creatinine)

Abbreviations: BUN, blood urea nitrogen; IP, intraperitoneal; KIM-1, kidney injury molecule-1; MDA, malondialdehyde; NAC: N-Acetylcysteine; PO, per oral; RCT, randomized controlled trial; TAC, total antioxidant capacity; TAU, taurine; ↓: decrease; ↑: increase.

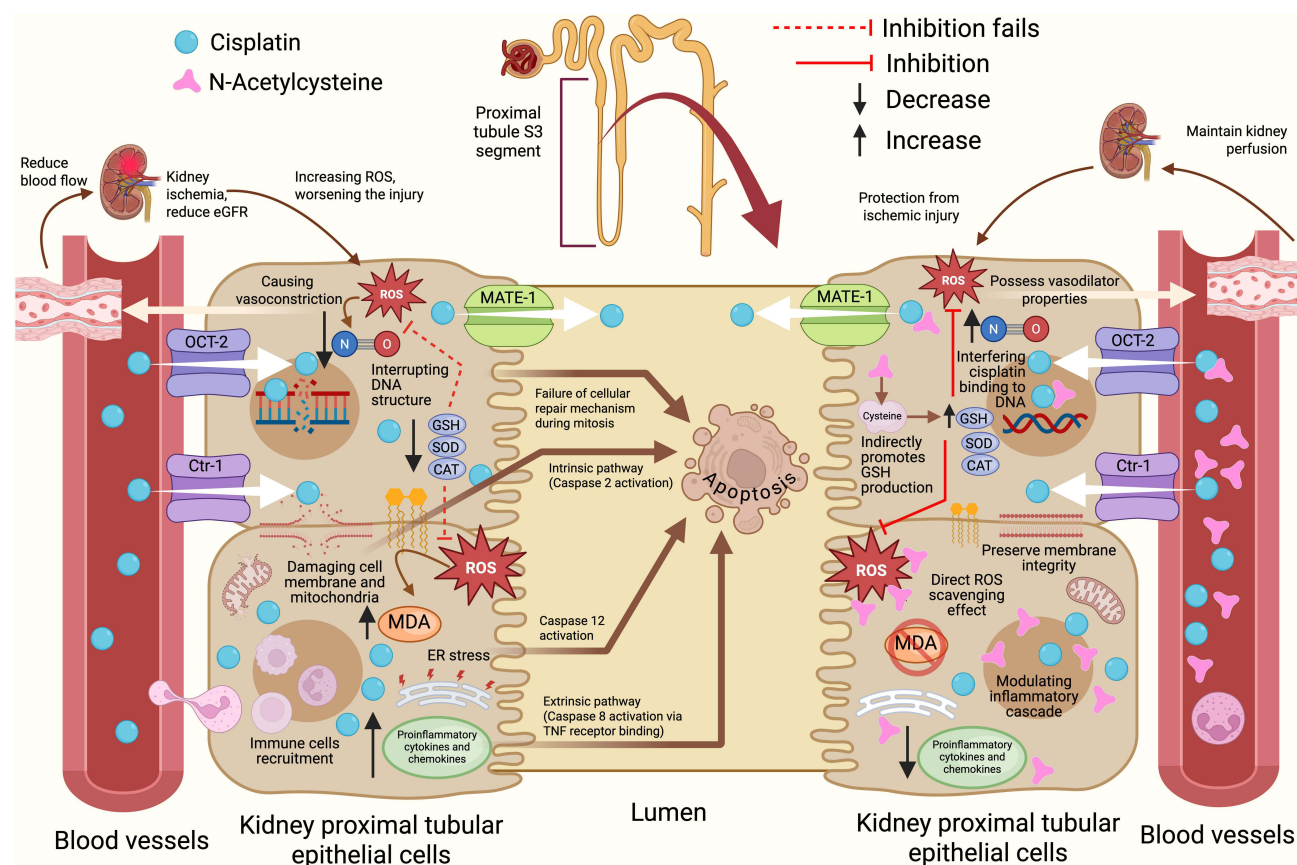


Figure 1 Pathogenesis of cisplatin-induced acute kidney injury (AKI) and mechanism of action of N-Acetylcysteine (NAC) as a nephroprotective agent (Created with BioRender.com).

Notes: Illustrates the mechanism happening inside of the renal tubular cells of S3 segment proximal tubules where cisplatin mostly accumulates, causing damage to the kidney and how N-acetylcysteine (NAC) potentially acts in preventing those damages. Subfigure 1A (the left side of the lumen) Pathogenesis of cisplatin-induced AKI. Subfigure 1A Description: Subfigure 1A illustrates how cisplatin enters renal tubular epithelial cells via organic cation transporter 2 (OCT-2) and copper transporter (Ctr-1), then exits via multidrug and toxin extrusion transporter 1 (MATE1) to the lumen. Inside the cells, cisplatin binds with DNA, disrupting the DNA structure and interrupting replication and transcription. This DNA damage and failure of the DNA repair mechanism during mitosis is one of the pathways leading to apoptosis. Cisplatin also reduces antioxidants (GSH, SOD, CAT) levels leading to reactive oxygen species (ROS) built up, causing oxidative stress. The oxidative stress causes lipid peroxidation, producing malondialdehyde (MDA) as a toxic byproduct that induces mitochondrial dysfunction, ER stress, apoptosis, and inflammation. This mechanism will also trigger cellular apoptosis via caspase 2, caspase 8, and caspase 12 activation. The renal tubular injury and hypoxia cause vasoconstriction, inducing renal ischemia and reducing eGFR. These mechanisms will further increase the ROS and worsen the injury. Subfigure 1B (the right side of the lumen) Mechanism of action of NAC as a nephroprotective agent in preventing cisplatin-induced AKI. Subfigure 1B Description: Subfigure 1B illustrates how NAC encounters cisplatin nephrotoxic mechanisms. NAC has antioxidant effects by directly scavenging ROS, replenishing intracellular GSH, increasing SOD and catalase activity, and decreasing lipid peroxidation and MDA levels. Moreover, it has an anti-inflammatory effect by reducing pro-inflammatory cytokines and NF- κ B activation. NAC cytoprotective effect comes from its ability to interfere with cisplatin binding to the DNA and to counter apoptosis by preserving mitochondrial integrity. Finally, by stabilizing nitric oxide, NAC reduces vasoconstriction and maintains renal perfusion. Therefore, preventing further damage from ischemic injury.

Abdel-Wahab et al⁶⁶ reported that in rats treated with NAC, urinary glucose and protein levels, lipid peroxidation (MDA), and enhanced antioxidant enzyme activities are significantly reduced.⁶⁶ Gunturk et al²⁶ also found that serum creatinine and BUN levels are significantly reduced in addition to renal histology improvement in the group treated with NAC (250 mg/Kg).²⁶ Similar observation has been reported by Huang et al²⁷ stating that cisplatin-treated mice show a reduction of inflammatory markers and neutrophil infiltration following NAC administration.²⁷ All these findings further strengthen the evidence of NAC's nephroprotective effect through antioxidant, anti-inflammatory, and cytoprotective mechanisms.

Up until now, clinical evidence remains inconsistent and limited. Visacri et al⁶⁸ in a randomized trial including patients with high-dose cisplatin, reported that administration of 600 mg NAC per oral showed no significant benefit in renal outcomes nor oxidative stress markers.⁶⁴ Meanwhile, Ibraheem et al and a study from Foundation University Islamabad reported the potential benefit of NAC in higher dosage and frequency. Still, the nephroprotective benefits

remain inconclusive. Limitations in getting reliable data from clinical trials are influenced by sample size, design, and population variation.^{27,67}

Discrepancies between preclinical and clinical outcomes happen due to variations in dosing, administration route, and study design. High-dose intravenous NAC is widely used in many preclinical studies. At the same time, clinical trials in humans favor oral formulation that might delay and reduce NAC's potent effects due to the lower bioavailability. Complicated interpretation because of several variations such as patient condition, hydration protocols and cisplatin regimen more likely to happen in clinical trials compared to animal studies that usually happen in a very controlled environment to limit confounding variables. Given NAC's promising efficacy and well-known safety, well-designed clinical trials are urgently needed to determine its therapeutic utility in oncology.

Future Directions and Clinical Implication

Further research on formulating ideal dosing strategies, timing, and administration routes is necessary to enhance NAC in preventing cisplatin-induced AKI without compromising the chemotherapeutic outcomes. Possible benefits of combining NAC with other nephroprotective agents, such as taurine or antioxidants, should be explored in order to create synergistic effects. There is an urgent need for conducting large-scale, double-blind, randomized controlled trials (RCTs) with standardized protocols to validate NAC's renal benefits across diverse cancer populations. While several studies have reported NAC's short-term nephroprotective effects, the potential effect in preserving long-term renal function after chemotherapy still needs further exploration.

Conclusion

N-acetylcysteine (NAC) is well known for its antioxidant, anti-inflammatory, and cytoprotective properties. These properties to neutralize reactive oxygen species, preserve tubular cell integrity, reduce inflammation, and prevent cell apoptosis has been consistently demonstrated in preclinical studies. These findings suggest that NAC may counteract key pathogenic pathways underlying cisplatin-induced acute kidney injury (AKI), supporting its potential as a nephroprotective agent.

However, translational studies confirming these robust preclinical findings in clinical practice remain limited. Due to several factors including variations in NAC dosing, route, and timing of administration, as well as differences in study design, patient populations, and outcome measures, current clinical trials have produced inconsistent outcomes. Consequently, while some trends toward reduced creatinine elevation or milder eGFR decline indicating preserved renal function have been recognized, no clear statistical difference nor consensus has been reached regarding NAC's efficacy in preventing cisplatin-induced AKI.

Regardless of these limitations, NAC remains an appealing potential nephroprotective agent due to its safety profile, availability, affordability, and established clinical use in other contexts such as acetaminophen toxicity and contrast-induced nephropathy. Further high-quality randomized controlled trials with standardized protocols are crucial to clarify its role, determine optimal administration regimens, and identify patient subgroups most likely to benefit. Establishing this evidence base is essential before NAC can be integrated into oncology practice as a nephroprotective strategy alongside cisplatin chemotherapy.

Acknowledgments

Figures depicting the mechanism of cisplatin-induced nephrotoxicity and the protective role of NAC were created using BioRender.com.

Disclosure

The author(s) report no conflicts of interest in this work.

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