Chemotherapy-induced oxidative injury in pediatric acute lymphoblastic leukemia: The role of N-acetylcysteine (Review)

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Abstract. Pediatric acute lymphoblastic leukemia (ALL) is the most common childhood malignancy. However, intensive chemotherapy frequently leads to notable organ toxicity, much of which is mediated by treatment-induced oxidative stress. Reactive oxygen species (ROS) generated during cytotoxic therapy contribute to tissue damage, including the liver, heart and nervous system. Current adjunctive therapies provide drug-specific protection, such as dexrazoxane for anthracycline-induced cardiotoxicity, but they do not address the shared ROS-generating pathway, a common mechanism of chemotherapy-induced toxicity across multiple agents and tissues. The present narrative review synthesizes the biochemical rationale, preclinical evidence and translational considerations for N-acetylcysteine (NAC) as a redox-modulating adjunct therapy in pediatric ALL. NAC acts as a glutathione precursor, scavenges reactive oxygen and nitrogen species, chelates redox-active metals, and modulates inflammatory signaling pathways. These properties have been associated with cytoprotective effects in preclinical models of chemotherapy-induced cardiotoxicity, hepatotoxicity, neurotoxicity and oxidative injury. Available evidence suggests that NAC can reduce treatment-related toxicity without consistently compromising antitumor efficacy, although outcomes appear to be dependent on timing, dosage and treatment context. While the favorable safety, low cost and accessibility of NAC support its potential clinical utility, current evidence remains limited, particularly in pediatric ALL populations. In conclusion, NAC represents a promising but context-dependent adjunctive strategy for mitigating chemotherapy-induced toxicity in pediatric ALL. Further well-designed clinical studies are required to define its optimal use, including timing, dosing and impact on oncological outcomes.

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Contents

1. Introduction

Pediatric acute lymphoblastic leukemia (ALL) is the most prevalent pediatric malignancy, representing ~25% of childhood cancers worldwide (1). Despite notable advances in risk-adapted treatment protocols, including stratification of patients into risk groups and optimizing chemotherapy selection and supportive care, the intensity and duration of multiagent chemotherapy regimens impose clinical and psychosocial burdens due to treatment toxicity. This toxicity is particularly relevant in children whose developing organ systems are susceptible to cytotoxic damage (2). Standard treatment protocols rely on agents such as vincristine, asparaginase, anthracyclines, methotrexate (MTX) and 6-mercaptopurine (6-MP). These agents are associated with specific off-target effects that contribute to acute and long-term complications, including hepatotoxicity, mucositis, neurotoxicity and cardiomyopathy (3). A number of these agents exert their cytotoxic effects, in part, by generating reactive oxygen species (ROS), which can also cause collateral tissue injury. These toxicities can disrupt adherence to treatment and compromise long-term survival. Current adjunctive strategies are limited to drug-specific antidotes, such as mesna for cyclophosphamide and leucovorin for MTX toxicity (4). However, these methods fail to adequately address the shared oxidative mechanisms underlying toxicity, specifically the accumulation of ROS and resulting oxidative stress, which are common consequences of chemotherapeutic agents used

in ALL treatment, including anthracyclines, vincristine and 6-MP. Therefore, there is a need for a broad-spectrum, clinically safe redox modulator in pediatric oncology (5).

N-acetylcysteine (NAC), a thiol-containing derivative of cysteine, is an established mucolytic agent and an antidote for acetaminophen poisoning. A review of preclinical studies indicates the capacity of NAC to replenish depleted glutathione stores, attenuate chemotherapy-induced oxidative stress, and protect against cellular damage across various organ systems, rendering NAC a promising candidate to address the need for a clinically safe redox modulator in ALL. The favorable safety profile, low cost and availability of NAC in oral and intravenous formulations support its potential for repurposing and integration into pediatric oncology regimens as an adjunct, particularly in resource-limited settings where long-term survival outcomes are increasingly prioritized (6). Therefore, the present review aims to synthesize the rationale and emerging evidence supporting NAC as a potential redox-modulating adjuvant in pediatric ALL. By examining the pharmacological actions of NAC in relation to common chemotherapeutic agents and their oxidative stress-related toxicity, the current review aims to evaluate whether NAC could improve treatment tolerability and survival without compromising the antileukemic efficacy of standard therapy, thereby providing a translational framework for future investigations and clinical applications.

2. Historical and pharmacological background

NAC is a synthetic N-acetyl derivative of cysteine, which is an endogenous amino acid involved in intracellular glutathione synthesis. NAC can be produced *in vitro* through chemical acetylation (7). Introduced in 1960, NAC was initially approved as an over-the-counter drug and mucolytic agent to relieve airway obstruction caused by excessive mucus production (8,9). The clinical applications of NAC have evolved from its initial use as a mucolytic agent to its established role as an antidote for acetaminophen toxicity (10) and, more recently, as a systemic antioxidant and redox modulator (Table I). In liver hepatocytes and renal cells, NAC is deacetylated to cysteine, which serves as a substrate for intracellular glutathione synthesis. This process replenishes glutathione depleted by the toxic metabolite N-acetyl-p-benzoquinone, thereby preventing hepatocellular injury (11). The role of NAC in this context underscores its dual capability to restore antioxidant reserves and directly neutralize reactive intermediates (12-14). These pharmacological mechanisms formed the basis for exploring the therapeutic potential of NAC under conditions driven by oxidative stress, including chemotherapy-induced toxicity. The following sections discuss these redox-modulating mechanisms in greater detail and their relevance to oncology.

3. Mechanisms of action relevant to oncology and translational potential

The clinical applications of NAC are based on redox-related mechanisms, which are particularly relevant in the context of chemotherapy-induced oxidative stress. NAC exerts its pharmacological effects primarily through its reactive thiol (-SH) group, which participates in redox reactions, including the reduction of disulfide bonds and free radical scavenging (15,16). These properties enable broader therapeutic applications beyond mucolysis. NAC can directly react with ROS and reactive nitrogen species, including hydroxyl radicals, nitrogen dioxide, nitric oxide and thiyl radicals (15). Another important feature of NAC is its ability to chelate heavy metals such as lead and mercury, as well as transition metals such as copper and iron, which helps prevent metal-catalyzed oxidative reactions that can induce organ toxicity (17). Queiroz de Andrade *et al* (18) and Pei *et al* (19) have shown that NAC decreases inflammation by inhibiting NF-κB activation and downregulating the expression of pro-inflammatory cytokines, such as TNF-α, IL-6 and IL-1β, thereby contributing to its potential antimutagenic and anticancer effects (20,21). The antimutagenic and anticancer effects of NAC are partly mediated through its anti-inflammatory properties, as chronic NF-κB-driven inflammation generates ROS, leading to DNA strand breaks and base modifications that promote mutagenesis and tumor progression (20,21).

NAC acts as a cysteine donor and glutathione precursor, replenishing the intracellular glutathione pools depleted by chemotherapy-induced oxidative stress (15,16). NAC also stabilizes mitochondrial function and maintains redox homeostasis through replenishing glutathione within the mitochondrial matrix and restoring the glutathione/glutathione disulfide ratio, thereby reducing lipid peroxidation and preserving cellular membranes. Through these mechanisms, NAC can mitigate organ damage, particularly in tissues susceptible to ROS-mediated injury, such as the liver, myocardium (22), peripheral nervous system (23) and bone marrow (23,24). Preclinical models and limited clinical studies have demonstrated that NAC can reduce chemotherapy-induced toxicity without substantially altering antitumor efficacy (25,26). In rat xenograft models of neuroblastoma and medulloblastoma, NAC reduced cisplatin-induced nephrotoxicity, as evidenced by blood urea nitrogen levels, without compromising antitumor efficacy when administered 4 h after the initial cisplatin dose (25). Pretreatment with NAC, however, significantly reduced chemotherapeutic effects. Ramezaninejad *et al* (26) also demonstrated in a clinical trial that oral NAC (1,200 mg) administered before a paclitaxel chemotherapy cycle reduced the incidence and severity of chemotherapy-related symptoms, as measured by standardized scales, including the Numeric Pain Rating Scale and the Neuropathy Pain Scale. These suggest that the protective effects are dependent on timing and may vary across chemotherapeutic agents, potentially interfering with ROS-dependent tumor cell killing, particularly when NAC is administered concurrently or prior to chemotherapy. However, administering NAC at an appropriately delayed interval may preserve antitumor efficacy while providing protection from adverse effects, supporting its potential as an adjuvant in pediatric ALL therapy.

4. ALL characteristics and treatment

ALL is a malignant hematopoietic disease characterized by the uncontrolled proliferation of immature lymphoid cells and their progenitor cells, leading to the replacement of normal elements in the bone marrow, including erythrocytes and platelets, peripheral blood and other organs, such as the lymph

Table I. Pharmacological evolution of the clinical use of N-acetylcysteine.

Clinical use	Primary mechanism	Clinical application	(Refs.)
Mucolytic agent	Reduction of disulfide bonds in mucoproteins through reactive thiol group, decreasing mucus viscosity	Treatment of respiratory conditions characterized by excessive mucus production	(8,9)
Antidote for acetaminophen toxicity	Replenishment of hepatic glutathione and detoxification of the reactive metabolite NAPQI, preventing oxidative liver injury	Standard treatment for acetaminophen overdose and acute liver injury	(10,11, 14)
Systemic antioxidant and redox modulator	Direct scavenging of reactive oxygen and nitrogen species, restoration of intracellular glutathione pools and modulation of redox signaling pathways	Conditions associated with oxidative stress, including chemotherapy-induced toxicity and other inflammatory disorders	(15,16, 18,19)

NAPQI, N-acetyl-p-benzoquinone.

nodes and spleen (27,28). ALL is classified into two subtypes based on its immunophenotype: T-cell ALL and B-cell ALL. Treatment for ALL comprises complex drug therapy and intensive programs and is divided into three phases: i) Induction, to achieve complete remission by eliminating the bulk of leukemic cells; ii) consolidation, which targets residual disease to prevent relapse; and iii) maintenance, which involves prolonged low-intensity therapy to sustain remission (4,27). The chemotherapy regimen broadly involves combinations of drugs such as vincristine, corticosteroids, asparaginase, cytarabine, MTX and 6-MP (4,27,29-31). The cytotoxic effects of these ALL treatments are also accompanied by treatment-related toxicity, including myelosuppression, gastrointestinal toxicity, neurotoxicity and hepatotoxicity, which is partly caused by ROS-mediated collateral injury (32,33).

Vincristine is an alkaloid derivative that exerts antineoplastic and immunosuppressive effects (34,35). Vincristine primarily targets microtubule formation, leading to depolymerization and cellular arrest or death (36). However, it also binds to microtubules and other cytoskeletal components, disrupting cellular transport. *In vitro* studies using mouse dorsal root ganglion neurons and induced pluripotent stem cell-derived human neurons have shown that vincristine disrupts mitochondrial dynamics, leading to increased ROS, mitochondrial fragmentation and axon degeneration (36,37), whereas studies in mouse models showed elevated ROS levels and increased apoptosis (37) Additional side effects of vincristine include myelosuppression (anemia, thrombocytopenia, bruising and bleeding), alopecia, nephrotoxicity and gastrointestinal toxicity (mucositis, nausea and vomiting) (38).

Anthracyclines are a group of non-selective antineoplastic drugs that promote the formation of superoxide anions and hydrogen peroxide, leading to oxidative DNA damage (39). For example, asparaginase is a widely used antimetabolite that degrades L-asparagine into aspartic acid and ammonia (40). In addition, this agent acts on the inositol trisphosphate signaling pathway, leading to the release of calcium ions and disruption of mitochondrial function. This process promotes mitochondrial permeability and markedly increases ROS production, ultimately leading to programmed cell death (41).

Antimetabolite agents, including cytarabine, 6-MP and MTX, predominantly exert their cytotoxic effects during the S phase of the cell cycle by interfering with DNA replication and nucleotide synthesis (42,43). The incorporation of cytarabine into DNA triggers replication stress, mitochondrial dysfunction and the formation of superoxides (44). Similarly, 6-MP produces thiol-containing metabolites that can be misincorporated into nucleic acids, thereby generating ROS (45). Furthermore, MTX inhibits folate metabolism, disrupts mitochondrial function, elevates homocysteine levels and reduces glutathione levels, thereby increasing ROS production (46). Together, antimetabolites generate ROS and deplete antioxidants, thereby inducing cytotoxicity against leukemic cells. However, these ROS-dependent mechanisms, although essential for antitumor activity, also contribute to treatment-related toxicity.

5. NAC as adjuvant therapy in ALL and other cancers

The treatment regimen for ALL is designed to eliminate leukemic cells, but is also associated with notable adverse effects. Common complications of treatment include infection, mucositis, diarrhea, acute hepatitis, allergic reactions, thrombotic reactions, hyperglycemia and neurotoxicity (47). Some of these complications, including hepatotoxicity, mucositis, neurotoxicity and myelosuppression (46), are associated with ROS-mediated damage and treatment outcomes (47). Based on this rationale, modulation of ROS and oxidative stress is a viable strategy to reduce these complications (Fig. 1). NAC has been evaluated as a redox-modulating adjunctive therapy in combination with chemotherapeutic agents (Table II). Across multiple tumor models, NAC consistently demonstrated protective effects against chemotherapy-induced toxicities, particularly nephrotoxicity associated with cisplatin and ifosfamide, and preserved hematologic parameters, such as white blood cell and platelet counts, in a lung cancer rat

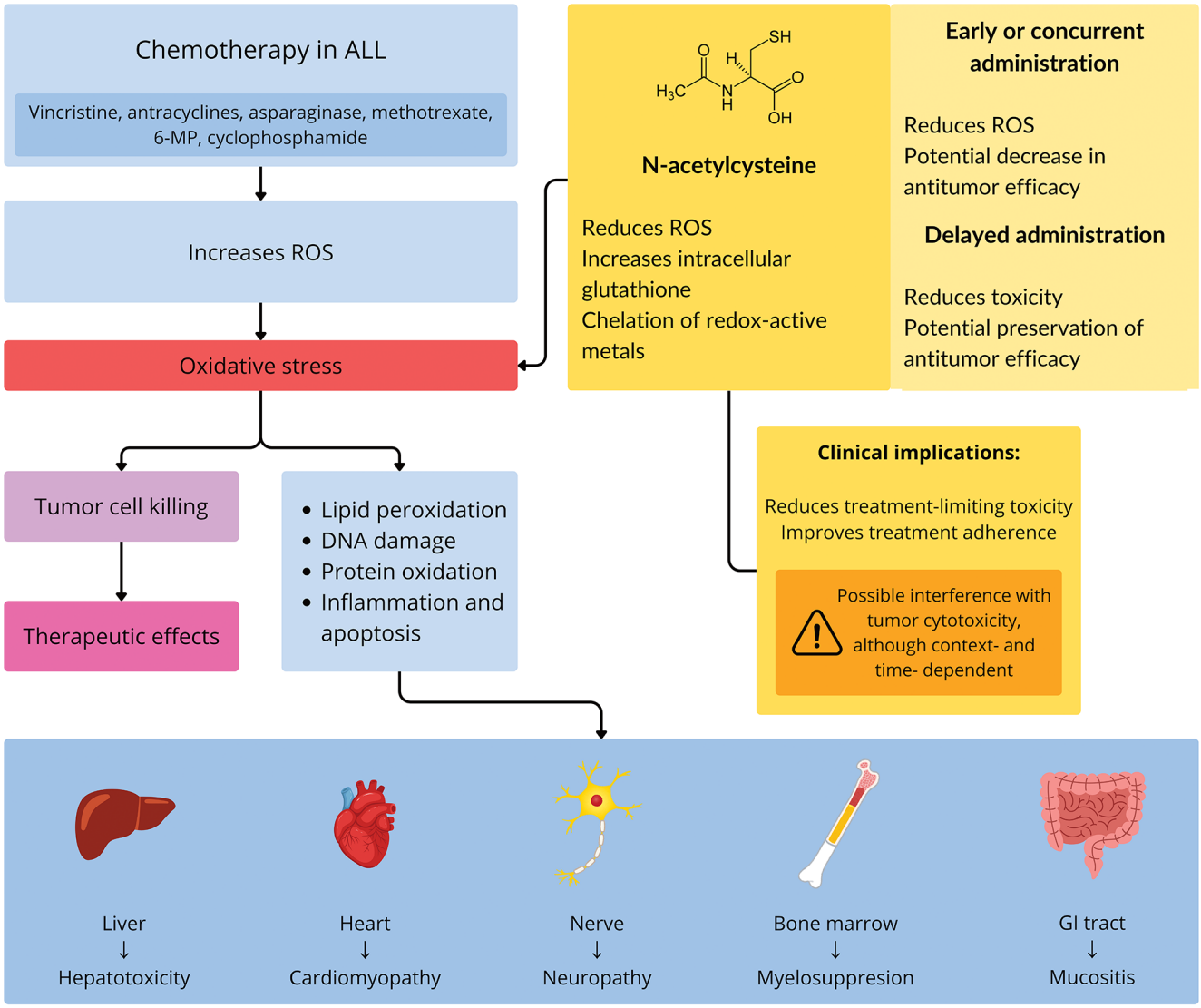

Figure 1. Chemotherapy-induced oxidative injury and timing-dependent effects of NAC. Chemotherapeutic agents used in ALL increase ROS levels, which are essential for tumor cell killing, but also cause off-target injury in several tissues, including the liver, heart, nervous system, bone marrow and GI tract. NAC acts as a redox-modulating agent and its effects are dependent on timing. Early or concurrent administration may reduce ROS-mediated cytotoxicity and potentially attenuate antitumor efficacy. By contrast, delayed administration may preserve therapeutic activity while reducing treatment-related toxicity. Thus, the application of NAC must be balanced by the potential interference with antitumor efficacy and also by protection from adverse effects in other organs. NAC, N-acetylcysteine; ROS, reactive oxygen species; GI, gastrointestinal; ALL, acute lymphoblastic leukemia.

model (24,48,49). Importantly, these studies reported that NAC did not compromise antitumor efficacy when administered concurrently with ifosfamide in *in vitro* models of neuroblastoma and rhabdomyosarcoma, and a mouse xenograft model of Ewing sarcoma (48,49). Furthermore, combination regimens incorporating NAC with other thiol agents preserved white blood cell and platelet counts without reducing chemotherapeutic effectiveness when temporal separation strategies, such as delaying the administration of NAC, were applied (24) However, evidence also indicates that the timing of NAC administration is critical, as early or concurrent administration may attenuate chemotherapy efficacy. By contrast, delaying administration of NAC, such as 4 h after the initiation of chemotherapy, preserves antitumor activity while maintaining cytoprotective effects (25). Collectively, these findings support the role of NAC as a context-dependent cytoprotective agent, with safety and efficacy largely determined by dosing schedule and treatment timing. These findings from non-ALL tumor models provide a rationale for considering NAC in pediatric ALL, where oxidative stress also contributes to treatment-related toxicity.

Several agents have been introduced as adjunct therapies (Table III). Mesna and leucovorin rescue are standard adjunctive therapies for cyclophosphamide and MTX (4). Mesna acts as a uroprotective agent by binding to acrolein, a toxic byproduct of cyclophosphamide, which can cause hemorrhagic cystitis (50,51). Leucovorin is a folic acid analog used to help restore DNA synthesis in cells inhibited by MTX (46). However, although drug-specific adjunctive treatments are approved for standard use (Table III), no therapy is available to address the shared oxidative stress mechanisms caused by the majority of chemotherapy drugs in ALL regimens (52).

Vincristine induces neurotoxicity that has been linked to oxidative stress and mitochondrial dysfunction. NAC may

Table II. Evidence of the effects of NAC on different chemotherapy agents.

Disease model	Chemotherapy regimens	Study type	Chemotherapy-induced adverse effect	Adjuvant agents	Effect of NAC on adverse effects	(Refs.)
Neuroblastoma/medulloblastoma xenograft	Cisplatin	Preclinical (rat tumor model)	Nephrotoxicity	NAC	Reduced nephrotoxicity, no interference with chemotherapy agent	(25)
Lung cancer brain metastasis model	Carboplatin, melphalan and etoposide	Preclinical (rat tumor model)	Myelosuppression (decreased white blood cells, platelets and granulocyte cell counts)	NAC, sodium thiosulfate	NAC preserved granulocyte count, NAC combined with sodium thiosulfate preserved white cells and platelet count	(24)
Neuroblastoma and rhabdomyosarcoma xenograft	Ifosfamide	Preclinical (mouse model)	Nephrotoxicity	NAC	Reduced nephrotoxicity, no reduction in antitumor efficacy	(48)
Ewing sarcoma xenograft	Ifosfamide	Preclinical (mouse model)	Nephrotoxicity	NAC	Reduced nephrotoxicity, no reduction in antitumor efficacy	(49)

NAC, N-acetylcysteine.

Table III. Adjunctive agents in pediatric ALL and other tumors.

Agent	Pharmacological class	Mechanism of action	Use in pediatric ALL and other tumors	(Refs.)
N-acetylcysteine	Broad-spectrum antioxidant	Glutathione precursor, ROS scavenger, NF-κB inhibitor and metal chelator	Potential multi-organ protection: Hepatotoxicity (asparaginase), neurotoxicity (vincristine), cardiotoxicity (anthracyclines), mucositis	(15-19,23, 25, 26, 56,61)
Dexrazoxane	Iron chelator (cardioprotective antioxidant)	Chelates iron, which prevents anthracycline-induced ROS formation	Prevention of anthracycline-induced cardiotoxicity	(54)
Mesna	Thiol uroprotective agent	Binds acrolein	Prevention of hemorrhagic cystitis	(50,51)
Leucovorin	Folate analogue (rescue agent)	Restores reduced folate pools, rescuing normal DNA synthesis after MTX treatment	Prevention of MTX toxicity	(46)

ALL, acute lymphoblastic leukemia; MTX, methotrexate; ROS, reactive oxygen species.

Table IV. Current evidence of NAC co-administration with chemotherapy agents used in acute lymphoblastic leukemia.

A, Vincristine

Study model	NAC administration	Chemotherapy-induced adverse effects	Effect of NAC on adverse effects	Effect on antitumor efficacy	(Refs.)
Vincristine-resistant lymphoblastoma (HOB1/VCR)	NAC co-treatment (20 mM)	Not evaluated	Not evaluated	Decreased cytotoxicity via suppression of ROS-mediated apoptosis	(71)
293T cells and MRP1-transfected tumor cells	NAC (1-5 mM) + vincristine	Not evaluated	Not evaluated	Increased drug resistance via the glutathione-dependent MRP1 pathway	(71)

B, Anthracyclines

Study model	NAC administration	Chemotherapy-induced adverse effects	Effect of NAC on adverse effects	Effect on antitumor efficacy	(Refs.)
Rat model of doxorubicin-induced cardiotoxicity	NAC 200 mg/kg i.p. daily (5 days) + doxorubicin 20 mg/kg i.p. single dose	Cardiotoxicity (increased TBARS, NO, AST, LDH and CK; decreased SOD and myocardial structural damage)	Decreased TBARS, NO, AST, LDH and CK; increased SOD and preserved myocardial architecture	Not evaluated	(22)
Clinical RCT (patients with breast cancer and lymphoma treated with doxorubicin or epirubicin)	NAC 1,200 mg orally q8 h per chemotherapy (doxorubicin or epirubicin) cycle	Cardiotoxicity (reduced LVEF and HF risk)	No notable protective effect on LVEF decline or clinical outcomes	Not evaluated	(55)
293T cells and MRP1-transfected tumor cells	NAC (1 and 5 mM) co-treatment with doxorubicin ± BSO	Not evaluated	Not evaluated	Decreased efficacy via glutathione-mediated drug resistance	(75)
Murine melanoma model (B16-F10)	NAC co-treatment (2 g/kg p.o.) with doxorubicin	Not evaluated	Not evaluated	No reduction in efficacy, possible synergistic antitumor effect	(74)

C, ASP

Study model	NAC administration	Chemotherapy-induced adverse effects	Effect of NAC on adverse effects	Effect on antitumor efficacy	(Refs.)
Rat model	NAC 200 mg/kg/day i.p. for 5 days (post-treatment after single-dose L-ASP 10,000 U/kg)	Liver and pancreatic injury: Histopathological damage (necrosis, congestion, cellular infiltration, acinar/islet injury)	Marked reduction in liver and pancreatic damage scores; histological improvement despite no notable change in MDA, GSH and CAT	Not evaluated	(60)

Table IV. Continued.

D, MTX

Study model	NAC administration	Chemotherapy-induced adverse effects	Effect of NAC on adverse effects	Effect on antitumor efficacy	(Refs.)
Rat experimental model	NAC 300 mg/kg/day + MTX (18 mg/kg/day)	Nephrotoxicity (increased MDA tubular damage, urea and creatinine; decreased SOD and GPx)	Decreased MDA, tubular damage, urea and creatinine; increased SOD and GPx	Not evaluated	(62)
B-cell lymphoma + renal cell model	NAC (0.2-0.4 mM) co-treatment	Not evaluated	Not evaluated	No reduction in antitumor activity	(64)

E, 6-Mercaptopurine

Study model	NAC administration	Chemotherapy-induced adverse effects	Effect of NAC on adverse effects	Effect on antitumor efficacy	(Refs.)
Primary Leydig cell culture	NAC co-treatment (dose not stated)	Increased ROS and Leydig cell apoptosis; reduced glutathione	Restored glutathione, reduced ROS and prevented cell death	Not evaluated	(65)
Clinical pilot crossover study (patients with IBD)	NAC 1,200 mg BID (oral) with thiopurine therapy	Liver injury, oxidative stress (increased MPO, MDA and F2-isoprostanes)	Reduced MPO, no improvement in liver enzymes or clinical hepatotoxicity	No effect on thiopurine metabolites or pharmacokinetics	(66)

F, Cytarabine

Study model	NAC administration	Chemotherapy-induced adverse effects	Effect of NAC on adverse effects	Effect on antitumor efficacy	(Refs.)
Adult rat model	NAC 200 mg/kg/day p.o. (pre + concurrent treatment for 14 days)	Cerebellar neurotoxicity: Impaired motor coordination, induced structural neuronal changes	Prevented behavioral deficits, preserved cerebellar structure	Not evaluated	(67)
Primary neuronal cell culture	NAC (1-30 μM, *in vitro*)	ROS-mediated neuronal apoptosis, DNA damage	Reduced ROS, DNA damage and apoptosis (dose-dependent protection)	Not evaluated	(63)

Table IV. Continued.

G, Cyclophosphamide

Study model	NAC administration	Chemotherapy-induced adverse effects	Effect of NAC on adverse effects	Effect on antitumor efficacy	(Refs.)
Rat model	NAC 200 mg/kg i.p. for 5 days (pre-treatment)	Cardiotoxicity (increased AST, ALT, CK, LDH, TNF-α, ADMA, NO and MDA; decreased SOD, catalase, GPx and GST activities)	Decreased AST, ALT, CK, LDH, TNF-α, ADMA, NO and MDA; increased SOD, catalase, GPx and GST activities	Not evaluated	(68)
Miniature pig model	Dietary NAC 0.5% (oral supplementation)	Reduced immune cell counts, increased liver injury (AST, ALT), TNF-α, IFN-γ, NF-κB, IL-8, IL-1β and oxidative stress (decreased SOD/GPx and increased MDA)	Increased immune cell counts, reduced liver injury (AST, ALT), TNF-α, IFN-γ, NF-κB, IL-8, IL-1β and oxidative stress (increased SOD/GPx and decreased MDA)	Not evaluated	(69)

NAC, N-acetylcysteine; DOX, doxorubicin; MTX, methotrexate; ASP, asparaginase; MRP1, multidrug resistance-associated protein 1; ROS, reactive oxygen species; TBARS, thiobarbituric acid reactive substances; MDA, malondialdehyde; GSH, glutathione; GPx, glutathione peroxidase; GST, glutathione S-transferase; SOD, superoxide dismutase; CAT, catalase; NO, nitric oxide; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; CK, creatine kinase; ADMA, asymmetric dimethylarginine; TNF-α, tumor necrosis factor-α; IFN-γ, interferon-γ; MPO, myeloperoxidase; LVEF, left ventricular ejection fraction; HF, heart failure; RCT, randomized controlled trial; CIPN, chemotherapy-induced peripheral neuropathy; IBD, inflammatory bowel disease; BSO, DL-buthionine (S,R)-sulfoximine; i.p., intraperitoneal; p.o., *per os*; q8 h, every 8 h; BID, twice daily.

help prevent oxidative stress by replenishing glutathione reserves in neuronal tissue. In a randomized controlled trial, Zhou *et al* (23) showed that NAC effectively reduces the incidence of CIPN and increases serum levels of nerve growth factor in breast cancer patients. Anthracyclines are another drug in the ALL regimen, which is associated with cardiotoxicity that is partially mediated by oxidative stress. NAC has been evaluated as a cardioprotective agent in rat models treated with doxorubicin, leading to reductions in markers of cardiotoxicity, such as creatine kinase and lactate dehydrogenase, and improved myocardial resistance (22). A case-control study by Khazdoz (53) showed reduced cardiotoxicity evident by decreased cardiac troponin levels in concurrent treatment of NAC and anthracycline in patients with breast cancer. However, the effects of NAC appear less consistent than those of dexrazoxane, which directly chelates iron to prevent ROS formation from anthracycline (54). A randomized controlled trial evaluating NAC administration on patients with breast cancer and lymphoma treated with doxorubicin or epirubicin showed no improvement in cardiotoxicity (55). Asparaginase-induced hepatotoxicity is associated with mitochondrial glutathione deficiency and, therefore, oxidative stress (56,57). Pre-clinical studies using rat models of non-alcoholic steatohepatitis and clinical studies in pediatric patients with ALL have shown that NAC administration can restore glutathione levels, improve fatty acid oxidation, and reduce inflammation (56,58,59). An animal study using rats further supported this, showing that NAC markedly reduced liver damage in the asparaginase-treated group (60).

Antimetabolite agents, including cytarabine, 6-MP and MTX, are integral therapies in ALL but are also associated with oxidative stress-related toxic effects (33). NAC may counteract these effects by restoring intracellular glutathione pools and stabilizing redox homeostasis (61). Studies have shown that NAC reduces MTX-induced hepatic and renal injury and increases antioxidant levels, including superoxide dismutase and glutathione in animal (62) and *in vitro* models (63) without causing reduction in antitumor activity (64), and reduces oxidative DNA damage caused by 6-MP (65,66) and cytarabine (63,67). Studies have also reported that NAC administration can mitigate the neurotoxicity associated with cytarabine metabolites (63) and decrease lipid peroxidation markers in patients with inflammatory bowel disease treated with 6-MP (66). Together, these findings support NAC as a biologically plausible adjunct for mitigating the oxidative complications across multiple chemotherapeutic agents.

6. Clinical considerations and challenges

The integration of NAC as a supportive adjunct in pediatric ALL therapy represents a promising but complex strategy. The ability of NAC to mitigate oxidative injury in hepatocytes, neurons and cardiomyocytes suggests its potential to reduce treatment-limiting toxicities. However, the impact of NAC on antileukemic efficacy remains context-dependent and requires careful consideration of timing and dosing (6). Compared with established agents, such as mesna, leucovorin and dexrazoxane, NAC represents a broader redox-modulating approach with potential multi-organ protective effects (Table III). However, its clinical role remains insufficiently defined and requires further validation in pediatric ALL.

Preclinical and clinical studies exploring NAC in ALL regimens have used different timing strategies in NAC administration including peri-infusion, prophylactic, concurrent and post-treatment (Table IV). This difference highlights the importance of timing as a determinant of potential interaction with antitumor efficacy. With regard to anthracyclines, the EPOCH randomized trial tested oral NAC administered before and after each infusion throughout all cycles but failed to show a notable difference in cardioprotection compared with the control group, suggesting that peri-infusion administration may not translate clinically (55). With regard to cytarabine, rat models were subjected to daily NAC administration starting before and continuing during exposure, which prevented cerebellar and behavioral toxicity, pointing to a prophylactic approach that is effective preclinically but remains untested in humans (67). Similarly, cell studies with 6-MP showed that concurrent NAC treatment restored glutathione levels and prevented oxidative injury, although the clinical implications remain uncertain owing to potential interference with cytotoxic efficacy (65). The combination of NAC with other chemotherapeutic agents has limited and context-specific effects. The use of NAC with cyclophosphamide and methotrexate is limited by established rescue agents (such as mesna and leucovorin) and potential antitumor interference (68,69). Evidence for asparaginase is limited to therapeutic case reports (56), and the optimal timing for managing vincristine-induced neuropathy remains unexplored (70). Preclinical studies suggest that NAC administered before or concurrently with cyclophosphamide may reduce acrolein-mediated toxicity, which mediates the side effects associated with cyclophosphamide use, including cardiotoxicity, liver damage and immunosuppression (50). Studies in animal models showed that NAC administration attenuates these side effects, as shown by increased immune cell counts and decreased cardiac and hepatic enzymes (68,69). However, concerns about potential interference with antitumor efficacy, along with the established use of mesna, limit the clinical applicability of NAC (68,69). With regard to MTX, experimental models indicate that NAC can provide protection by increasing antioxidant enzyme activities (superoxide dismutase and glutathione peroxidase) when administered before or during exposure, resulting in decreased malondialdehyde levels, tubular damage and urea and creatine levels (62). However, similar to cyclophosphamide, leucovorin is already the standard rescue therapy for MTX-related toxicity. By contrast, evidence for asparaginase is primarily derived from case reports in which NAC was administered after the onset of hepatotoxicity, suggesting a therapeutic rather than preventive role (56). Preclinical evidence further supports this finding, with NAC administration reducing asparaginase-induced liver and pancreatic damage in a rat model (60). With regard to vincristine, no studies have evaluated NAC timing for neuropathy, and current management remains limited to symptomatic treatment (70). However, concerns exist for combining NAC with vincristine, as multiple preclinical studies have shown decrease in cytotoxicity and increase in drug resistance (71,72). Overall, while preclinical evidence supports the cytoprotective potential of NAC, its interaction with antitumor efficacy

remains uncertain, as most evidence of NAC effectiveness comes from *in vitro* studies. These uncertainties highlight the need for pharmacokinetic and timing-based studies to define its safe clinical use.

Table IV summarizes the current evidence on NAC co-administration across major chemotherapeutic agents used in ALL. However, the evidence is heterogeneous, with frequent reports of reduced cytotoxicity in *in vitro* experiments and limited preclinical animal model and clinical data, especially on therapeutic outcomes. This highlights the importance of interpreting current evidence in the context of NAC-chemotherapy-related interactions. One of the major factors influencing NAC's effects is the timing of NAC administration, as concurrent antioxidant exposure to cytotoxic agents that utilize ROS-mediated mechanisms may theoretically reduce tumor cytotoxicity (5). Early or concurrent administration has been associated with reduced cytotoxicity (73). For example, NAC pretreatment prior to cisplatin significantly reduced chemotherapeutic efficacy in rat neuroblastoma and medulloblastoma xenograft models (25). Additionally, concurrent treatment of NAC and doxorubicin in HOB1/VCR lymphoma cells *in vitro* attenuated doxorubicin-induced cytotoxicity (71). Furthermore, delayed administration of NAC up to 4 h after cisplatin preserved antitumor efficacy while providing protection against kidney damage (25). Similarly, therapeutic use of NAC after the onset of toxicity, as observed in clinical reports of asparaginase-associated hepatotoxicity, appears to provide organ protection without compromising treatment efficacy (56). Together, these findings indicate that NAC timing is critical to both safety and effectiveness.

Aside from mitigating damage from treatment toxicity, NAC has also shown interactions with anticancer therapies, including inhibition of tumor growth and modulation of signaling pathways. NAC has been shown to inhibit NF-κB and downregulate the expression of pro-inflammatory cytokines. In a murine melanoma model, co-administration of NAC with doxorubicin has shown synergistic antitumor effects (74), whereas other studies revealed that NAC increases doxorubicin resistance in multidrug resistance-associated protein 1-transfected tumor cells (75) and decreases cytotoxicity in the vincristine-resistant lymphoblastoma model (71). A systematic review reported no marked decrease in antitumor efficacy, with some studies suggesting improved outcomes potentially due to better treatment tolerability (76). However, these findings remain inconsistent, and there is currently insufficient evidence to support a synergistic role of NAC in enhancing antitumor efficacy in ALL. Evidence on NAC co-administration in ALL is limited, largely derived from *in vitro* and preclinical models. In addition, variability in toxicity suggests that some patients may benefit more from NAC administration than others (5). Furthermore, long-term outcomes, including relapse rates, minimal residual disease and overall survival, have not been evaluated. These gaps need to be addressed through studies and clinical trials before NAC use in pediatric ALL can be applied in clinical settings.

7. Future directions

Further investigation is required to define the optimal timing, route and dosage of NAC in relation to specific chemotherapeutic agents, particularly given that oxidative mechanisms partially mediate their action. Considering the importance of timing, pharmacokinetic and pharmacodynamic studies are needed to identify the optimal therapeutic window for NAC protection without compromising treatment efficacy. Studies should assess redox biomarkers, such as glutathione, lipid peroxidation and inflammatory cytokines, as well as organ-specific injury markers, including liver transaminases, cardiac troponin and neurofilament proteins, to evaluate toxicity and therapeutic impact. Future studies should also evaluate NAC on oncological outcomes, including treatment adherence, dose intensity, minimal residual disease, relapse rates and long-term survival. Comparative trials examining prophylactic and delayed NAC administration are necessary to optimize its potential clinical use. Given the variability in patient susceptibility, an individualized approach may be required. Together, future research on these aspects is essential to establish evidence-based strategies for NAC use in pediatric oncology.

In conclusion, the integration of NAC as a toxicity-modifying adjunct in pediatric ALL requires careful consideration of its pharmacological interactions, timing and patient-specific factors. While existing evidence supports the potential of NAC to protect organs, its impact on antileukemic efficacy remains poorly defined. Clinical studies are necessary to determine the safety, efficacy and optimal timing for the integration of NAC into treatment protocols. Until such evidence is available, NAC use should remain investigational and guided by prospective studies.

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Use of artificial intelligence tools

During the preparation of this work, artificial intelligence tools (Grammarly) were used to improve the readability and language of the manuscript or to generate images, and subsequently, the authors revised and edited the content produced by the artificial intelligence tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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