Optimization Of Intensive Care For Nephro- And Hepatotoxicity Of Lung Cancer Chemotherapy

Ergashev Nuriddin Hamzaevich *Tashkent State Medical University, Uzbekistan*

Gaziev Zoir Takhirovich *Tashkent State Medical University, Uzbekistan*

Umarova Kamola Ravshanovna *Tashkent State Medical University, Uzbekistan*

ABSTRACT

Lung cancer remains the leading cause of cancer mortality worldwide, and systemic chemotherapy is a cornerstone of treatment for advanced stages. However, many chemotherapeutic agents used in lung cancer can cause significant nephrotoxicity and hepatotoxicity, which may limit therapy, necessitate dose reductions, or even lead to life-threatening organ failure. Cisplatin-based regimens, for example, are highly effective but carry a well-documented risk of acute kidney injury (AKI) due to proximal tubular damage, electrolyte disturbances, and reduced glomerular filtration. Likewise, various cytotoxic drugs can induce liver injury in idiosyncratic patterns ranging from transient asymptomatic transaminase elevations to fulminant hepatic failure. Optimizing intensive care management of these toxicities is essential to ensure patients can safely continue potentially curative treatments. This narrative review summarizes the nephrotoxic and hepatotoxic effects of common lung cancer chemotherapeutic agents and discusses strategies to prevent and mitigate these toxicities

Keywords: Lung cancer; chemotherapy; nephrotoxicity; hepatotoxicity

INTRODUCTION

Lung cancer is a significant global health concern, accounting for an estimated 1.8 million deaths in 2020 – the highest of any malignancy. While recent advances such as targeted therapies and immune checkpoint inhibitors have improved outcomes in certain subsets of lung cancer, platinum-based combination chemotherapy remains a mainstay of treatment for the majority of patients with advanced disease. Unfortunately, the use of these cytotoxic agents is limited by their narrow therapeutic index and potential to cause serious multi-organ toxicity. In particular, damage to the kidneys (nephrotoxicity) and liver (hepatotoxicity) are among the most critical adverse effects, as these can not only compromise vital organ function but also necessitate chemotherapy dose delays or discontinuation.

Nephrotoxicity is a well-recognized dose-limiting toxicity of several first-line lung cancer chemotherapeutics. Cisplatin, in particular, is one of the most nephrotoxic agents widely used in oncology. It induces apoptosis and necrosis of renal tubular cells via DNA cross-linking, oxidative stress, and inflammation, leading to acute kidney injury (AKI) characterized by reduced glomerular filtration rate (GFR), electrolyte wasting (e.g. hypomagnesemia), proximal tubular dysfunction (Fanconi syndrome), and even thrombotic microangiopathy. Other drugs commonly used in lung cancer, such as antimetabolites (e.g.

pemetrexed and gemcitabine) and topo-isomerase inhibitors (etoposide), can also contribute to renal impairment through mechanisms like tubular crystal precipitation, afferent arteriolar vasoconstriction, or glomerular endothelial injury. The development of chemotherapy-induced AKI poses substantial risks, including interruptions in cancer treatment, prolonged hospitalization, need for renal replacement therapy, and increased mortality. Indeed, cisplatin alone has been reported to account for roughly 20% of chemotherapy-related AKI cases in hospitalized cancer patients. Patient-related factors such as advanced age, baseline renal insufficiency, diabetes, hypertension, and volume depletion further heighten the susceptibility to drug-induced nephrotoxicity. Given that a large proportion of lung cancer patients present with reduced renal function at diagnosis (in one cohort, over 50% had GFR <90 mL/min/1.73 m^2), careful management of nephrotoxic risk is imperative [1, 2].

MATERIALS AND METHODS

A narrative literature review was conducted to gather data on chemotherapy-induced nephrotoxicity and hepatotoxicity in lung cancer and on supportive care measures to optimize patient outcomes. Relevant articles were identified through searches of PubMed, Scopus, and Web of Science up to November 2025, using keywords such as "lung cancer chemotherapy toxicity," "cisplatin nephrotoxicity," "chemotherapy-induced liver injury," and "supportive care for chemotherapy toxicity." Priority was given to recent publications (within the last 5–7 years) including clinical trials, cohort studies, consensus guidelines, and review articles focusing on organ-specific toxicities of lung cancer treatments. Classic reference articles on foundational concepts (e.g. mechanisms of cisplatin nephrotoxicity) were also included for background. We included English-language papers and also drew on international guidelines (e.g. oncology and critical care societies) when available. Since this study is a narrative review without patient-level data, no formal ethical approval was required. The findings were synthesized qualitatively, and no statistical meta-analysis was performed. Instead, the authors integrated the evidence into a coherent discussion organized by organ system (renal vs hepatic toxicity) and management strategies. All sources used are cited in GOST style in the References section [3].

RESULTS AND DISCUSSION

Incidence and Mechanisms of Chemotherapy-Induced Nephrotoxicity: Nephrotoxicity is among the most frequent serious adverse effects of conventional chemotherapy in lung cancer patients. AKI occurs in up to 20–30% of patients receiving certain chemotherapeutic agents despite preventive measures, and can lead to considerable morbidity and mortality. Cisplatin, a platinum-based alkylating agent, is notoriously nephrotoxic and has been extensively studied in this regard. It accumulates in renal proximal tubular cells, causing DNA cross-linking and activating pro-apoptotic pathways (e.g. p53, caspases) that result in tubular cell death. Cisplatin also triggers inflammation and oxidative stress in the kidney, leading to injury of renal vasculature and a reduction in GFR. Clinically, cisplatin nephrotoxicity typically presents as AKI with non-oliguric acute tubular necrosis, accompanied by electrolyte disturbances such as hypomagnesemia and hypokalemia due to renal wasting. Fanconi syndrome (proximal tubule dysfunction with bicarbonaturia, phosphaturia, and glycosuria) may occur in severe cases, and some patients develop features of thrombotic microangiopathy (TMA) – characterized by hemolytic anemia, thrombocytopenia, and renal failure – either directly from cisplatin or due to synergistic effects of cancer itself. Fortunately, cisplatin-induced AKI is often reversible if recognized early and the drug is withheld, although repeated injury can lead to chronic interstitial fibrosis and permanent loss of renal function [4].

Carboplatin, a platinum analog frequently substituted for cisplatin in lung cancer regimens (especially for patients with comorbidities), is considered less nephrotoxic than cisplatin. Carboplatin's dose is typically calculated based on renal function (Calvert formula using creatinine clearance), which helps mitigate

excessive exposure. Nonetheless, carboplatin can still cause AKI at high doses or in predisposed patients, by a mechanism of cumulative tubular cell toxicity and occasional TMA similar to cisplatin. Thus, vigilant renal monitoring is necessary even with carboplatin.

Other non-platinum chemotherapeutic agents used in lung cancer also have notable nephrotoxic potential. Pemetrexed, an antifolate antimetabolite indicated for non-squamous non-small cell lung cancer (NSCLC), is primarily eliminated by the kidneys and can induce renal injury especially if accumulation occurs. Pemetrexed has been associated with reversible AKI in some patients, and rare cases of irreversible renal failure with interstitial nephritis and fibrosis despite drug discontinuation have been reported. High-dose methotrexate (a related antifolate used in other cancers) is a classic cause of crystal nephropathy due to precipitation in renal tubules, but pemetrexed at standard doses is less prone to crystallize; nonetheless, dehydration or drug interactions could potentially precipitate a similar issue, so maintaining adequate hydration is advised. Gemcitabine, a nucleoside analogue commonly used for NSCLC (especially squamous cell carcinoma) and small cell lung cancer, usually has mild renal effects but is known to cause a rare yet devastating complication: hemolytic uremic syndrome (HUS) or thrombotic microangiopathy [5]. Gemcitabine-induced HUS/TMA typically presents after multiple cycles with hypertension, edema, anemia, thrombocytopenia, and acute kidney injury with proteinuria. Although uncommon, this condition carries a high risk of progression to end-stage renal disease if not recognized; discontinuation of gemcitabine is mandatory, and therapeutic plasma exchange or complement inhibition with eculizumab (which has shown success in case reports) may be employed to treat the TMA. Other agents such as the anti-VEGF antibody bevacizumab (used in some NSCLC combinations) can also contribute to nephrotoxicity by causing hypertension, proteinuria, and a thrombotic microangiopathy due to inhibition of VEGF signaling in glomerular endothelial cells, highlighting that targeted therapies have renal effects too.

Etoposide (a topoisomerase II inhibitor used in small cell lung cancer) is primarily cleared by the liver and kidneys; in renal impairment, etoposide can accumulate and exacerbate myelosuppression and mucositis, but direct nephrotoxicity is not prominent. Still, dose reduction of etoposide is recommended in patients with significantly reduced creatinine clearance to avoid indirect kidney stress from tumor lysis or sepsis. Risk factors for chemotherapy-associated AKI include many host factors and comorbidities. Older age (over 60) is consistently associated with higher nephrotoxic risk, as renal reserve declines with age. Baseline renal insufficiency (e.g. GFR <60 mL/min/1.73 m^2) is a strong predictor of further kidney injury during treatment. Other common risk factors are diabetes mellitus, underlying hypertension, heart failure (reducing renal perfusion), concurrent use of other nephrotoxic medications (e.g. NSAIDs, iodinated contrast, certain antibiotics), and volume depletion or sepsis during therapy. Many of these factors often co-exist in lung cancer patients, who tend to be older with significant smoking histories and comorbid conditions. For instance, a large prospective study found that only one-third of patients with solid tumors (including lung cancer) had a normal GFR ≥90 mL/min at diagnosis, while the rest had moderate to severe renal impairment. This underscores the importance of assessing renal function before chemotherapy and accounting for it in regimen selection and dosing [6].

Clinical Impact: The consequences of untreated or severe nephrotoxicity during lung cancer chemotherapy are profound. Acute kidney injury not only causes immediate morbidity – with symptoms ranging from fatigue and decreased urine output to electrolyte imbalances and uremia – but also can delay or preclude further cancer therapy. Treatment interruptions due to AKI can allow tumor progression and negatively impact survival. In-hospital mortality for cancer patients who develop chemotherapy-associated AKI has been reported around 15%, and nearly half of such

patients may not recover their baseline renal function. Moreover, even subclinical renal function declines can limit options for subsequent lines of therapy, as many second-line agents (and supportive medications) also require renal clearance. Therefore, proactive strategies to minimize nephrotoxicity are critical in the intensive care of oncology patients [7].

Patterns and Mechanisms of Chemotherapy-Induced Hepatotoxicity: Chemotherapy-related liver injury encompasses a broad array of patterns, reflecting the diverse mechanisms by which anticancer drugs can affect hepatocytes and the hepatic microenvironment. Unlike the kidney, which often sustains injury from direct tubular toxicity of unchanged drugs or precipitated metabolites, the liver typically faces the challenge of drug metabolism and immune-mediated reactions. Most chemotherapy-induced hepatotoxicity is idiosyncratic, meaning it is not strictly dose-dependent nor predictable, and it can manifest after variable exposure durations. Drug-induced liver injury (DILI) in cancer patients is in fact a leading cause of chemotherapy dose reductions or cycle delays. The liver's central role in metabolizing xenobiotics predisposes it to collateral damage from chemotherapy: toxic metabolites, reactive oxygen species, and immune-mediated attack on drug-altered hepatic cells all contribute to injury.

Common presentations of chemo hepatotoxicity include acute hepatocellular injury (resembled by elevations in AST, ALT), cholestatic injury (elevated alkaline phosphatase and bilirubin with pruritus or jaundice), or a mixed pattern. Additionally, certain chemotherapy agents cause distinct forms of liver pathology. For example, oxaliplatin (used in gastrointestinal cancers) is well known to produce sinusoidal endothelial damage in the liver, leading to sinusoidal obstruction syndrome (veno-occlusive disease) with hepatomegaly, ascites, and portal hypertension. While oxaliplatin is not a standard lung cancer drug, similar vascular or sinusoidal injuries have been observed with other agents occasionally. Methotrexate, at chronic low doses (for rheumatoid arthritis) can cause hepatic fibrosis and cirrhosis over time, and at high doses can cause acute toxic hepatitis; however, methotrexate is not commonly used in lung cancer therapy. Gemcitabine, as noted, usually causes only transient transaminase elevations in ~20–30% of patients which normalize after discontinuation, but it has been implicated in rare cases of severe cholestatic hepatitis and hepatic failure, particularly in patients with underlying liver disease or in combination therapies. Docetaxel and paclitaxel are metabolized by hepatic CYP enzymes and frequently cause mild elevations of liver enzymes during treatment (Grade 1–2 hepatotoxicity). Clinically significant hepatotoxicity from taxanes is uncommon in patients with normal baseline liver function, but can be pronounced in those with hepatic impairment; hence dose adjustments are recommended and treatment is contraindicated if bilirubin is above the normal range due to risk of fatal toxicity. Vinorelbine, a vinca alkaloid often used in NSCLC, has a similar profile where mild transient LFT elevations are noted and severe liver injury is rare. It is primarily cleared by the liver, so toxicity is heightened in hepatic dysfunction [8].

An important aspect of chemotherapy hepatotoxicity is the potential for reactivation of hepatitis viruses. Cytotoxic chemotherapy can lead to immunosuppression that allows latent hepatitis B virus (HBV) to replicate dramatically, sometimes causing a fulminant hepatitis when the immune system recovers (immune reconstitution). This is not a direct toxic effect of the chemo agent on hepatocytes, but rather an indirect effect of treatment on viral dynamics. Patients with chronic HBV who receive chemotherapy for lung cancer (or any cancer) should be identified before therapy and started on antiviral prophylaxis to prevent such events, as chemotherapy-induced HBV reactivation carries a high risk of liver failure. Similarly, hepatitis C virus (HCV) positive patients can experience flares of hepatitis during treatment. Therefore, guidelines often recommend screening for HBV/HCV in cancer patients undergoing intense chemotherapy, although this is a preventive measure beyond the intrinsic drug toxicity.

Immune-mediated hepatotoxicity deserves mention, as modern lung cancer regimens frequently incorporate immunotherapies. While not "chemotherapy" in the classic sense, immune checkpoint inhibitors (e.g. pembrolizumab, nivolumab, atezolizumab) given alone or with chemo can cause immune-related adverse events. Hepatitis due to checkpoint inhibitors generally presents with a hepatocellular pattern of injury (marked ALT/AST elevations) and histology resembling acute autoimmune hepatitis (T-cell infiltration of the liver). The incidence of grade 3–4 immune-related hepatitis in trials is around 5% or less, but real-world data indicate higher rates especially when immunotherapy is sequentially combined with other hepatotoxic treatments. Management of these cases differs, involving high-dose corticosteroids and immunosuppressants rather than conventional supportive measures. Nonetheless, the presence of immunotherapy in many lung cancer treatment protocols means clinicians must be vigilant for hepatic toxicity from either modality [9].

CONCLUSION

The nephrotoxic and hepatotoxic side effects of lung cancer chemotherapy present significant challenges in oncology practice, but with diligent preventive and intensive care strategies, these toxicities can be managed and, in many cases, mitigated. Chemotherapy agents such as cisplatin, carboplatin, pemetrexed, gemcitabine, and docetaxel each carry distinct risks to the kidneys and liver that warrant careful consideration. Key principles include thorough baseline assessment of renal and hepatic function, routine monitoring during treatment, and early intervention at the first signs of organ injury. Aggressive hydration and nephroprotective measures have proven effective in reducing the incidence of cisplatin-induced AKI, while close LFT surveillance and timely dose modifications can prevent mild hepatotoxicity from escalating to liver failure. In the event of severe toxicity, a prompt multidisciplinary response – involving oncologists, intensivists, nephrologists, and hepatologists – is essential to support the patient with measures such as dialysis, corticosteroids for immune-mediated damage, or other organ-supportive therapies. Most chemotherapy-related kidney and liver injuries are reversible if addressed early, underscoring the importance of vigilance and patient education.

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