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| ARTICLE REVIEW

The Role of Neutrophil Gelatinase-Associated Lipocalin (NGAL) in the Early Detection of Nephrotoxicity caused by Chemotherapy for Breast Cancer

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| ABSTRACT
Chemotherapy remains a cornerstone of breast cancer management; however, its potential to induce renal injury continues to pose substantial clinical challenges. Early identification of kidney impairment is essential to prevent irreversible damage and to maintain the safety and continuity of cancer treatment. Conventional indicators such as serum creatinine and estimated glomerular filtration rate (eGFR) lack sufficient sensitivity because they typically increase only after considerable nephron loss has occurred. Neutrophil gelatinase-associated lipocalin (NGAL) has emerged as a promising early biomarker for renal injury Synthesized by renal tubular epithelial cells and neutrophils in response to tissue damage, NGAL levels can rise within hours following exposure to nephrotoxic agents. This review examines the role of NGAL in detecting chemotherapy-related nephrotoxicity among breast cancer patients, drawing on evidence from both clinical and experimental studies. Post-chemotherapy elevations in NGAL frequently precede detectable changes in serum creatinine, highlighting its capacity to identify subclinical tubular injury. Nonetheless, additional prospective studies employing standardized measurement protocols are needed to further validate the diagnostic accuracy and clinical utility of NGAL.

| KEYWORDS

NGAL, nephrotoxicity, chemotherapy, breast cancer, biomarker.

| ARTICLE INFORMATION

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1. Introduction

Breast cancer is the most common malignancy in women and the leading cause of cancer-related deaths worldwide. Based on GLOBOCAN 2022 data, over 2.3 million new cases are reported annually, with the disease burden continuing to increase, especially in developing countries. Treatment options for breast cancer can include surgery, radiation therapy, chemotherapy, and immunotherapy, all tailored to each patient's specific circumstances, health status, and preferences (Wang, et al., 2023). Chemotherapy remains the primary modality in the management of breast cancer, whether as adjuvant, neoadjuvant, or for metastatic disease. However, systemic side effects from chemotherapy often limit its effectiveness. One important complication to be aware of is nephrotoxicity. Kidney damage caused by chemotherapy can lead to impaired excretory function, electrolyte imbalances, and even acute kidney failure. Cytotoxic agents such as anthracyclines, taxanes, and platinum-based compounds are known to cause renal tubular injury through various mechanisms, including oxidative stress, inflammation, and apoptosis of tubular epithelial cells. Early detection of kidney damage is crucial to prevent the progression of damage and adjust chemotherapy regimens to ensure safety (Yoon, *et al.,* 2022). Conventional biomarkers such as serum creatinine and glomerular filtration rate (GFR) have limitations because they only increase after significant kidney damage has occurred. This has led to a need for biological markers that are more sensitive to early kidney injury. Neutrophil Gelatinase–Associated Lipocalin (NGAL), which will be written as NGAL from now on, has emerged as a promising candidate biomarker because its increase can be detected within hours of exposure to nephrotoxic agents (Zhao, *et al.,* 2021). This review aims to clarify the biological basis, pathophysiological mechanisms, and clinical evidence regarding the role of NGAL as an early marker of nephrotoxicity due to chemotherapy in breast cancer patients.

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2. Definition

Neutrophil Gelatinase-Associated Lipocalin (NGAL) is a 25kDa protein belonging to the lipocalin family. It was first identified in neutrophil granules and is involved in iron transport through siderophore binding (Lima, et al., 2020). Under normal physiological conditions, NGAL is expressed at low levels in several tissues, including the kidneys, lungs, liver, and gastrointestinal tract (Yoon, et al., 2022). However, it is expression increases sharply in response to tissue injury, infection, or inflammation (Zhao, et al., 2021). In the kidneys, NGAL is produced by both proximal and distal tubular epithelial cells (Lima, et al., 2020). Following tubular injury, NGAL is released rapidly into the bloodstream and urine, functioning as a sensitive indicator of structural kidney damage (Yoon, et al., 2022). NGAL levels may rise within 2-6 hours after kidney injury, significantly earlier than changes in serum creatinine (Zhao, et al., 2021). This makes NGAL a promising early biomarker for detecting renal impairment, including chemotherapy-induced nephrotoxicity (Lima, et al., 2020).

3. Epidemiology

Nephrotoxicity is a major adverse effect of chemotherapy and may affect up to 30% of cancer patients, depending on the specific drug and patient factors (Yoon, et al., 2022). Among chemotherapeutic agents, platinum-based compounds-especially cisplatin, are associated with the highest rates of nephrotoxicity, reported in approximately 20-4-% of patients (Donderski, et al., 2023). Other agents such as doxorubicin, paclitaxel, and cyclophosphamide have also been implicated in varying degrees of renal dysfunction (Yoon, et al., 2022). In breast cancer patients, the risk of nephrotoxicity increases because combination chemotherapy regimens are frequently used to enhance antitumor efficacy (Donderski, et al., 2023). Comorbidities such as hypertension, diabetes mellitus, and advanced age further heighten vulnerability to kidney injury (Yoon, et al., 2022). Nephrotoxicity incidence is also higher in developing countries, where limitations in renal monitoring and early detection contribute to delayed identification of kidney injury (Lima, et al., 2020).

4. Etiology

Chemotherapy-induced nephrotoxicity results from both direct and indirect injury to renal tubular epithelial cells (Yoon, et al., 2022). Platinum-based agents, particularly cisplatin, are the most frequently implicated due to their preferential accumulation within proximal tubular cells (Donderski, et al., 2023). Cisplatin uptake occurs primarily through organic cation transporter 2 (OCT2), which facilitates intracellular accumulation and subsequent cytotoxicity (Yoon, et al., 2022). Anthracyclines, including doxorubicin, contribute to nephrotoxicity through mechanisms involving oxidative stress, mitochondrial dysfunction, and endothelial injury (Yoon, et al., 2022). Taxanes such as paclitaxel may exacerbate renal impairment through systemic inflammatory activation and microvascular dysfunction (Yoon, et al., 2022). Patients with pre-existing comorbidities, including hypertension, diabetes mellitus, and chronic kidney disease, demonstrate heightened vulnerability to chemotherapy-related renal injury (Ameer, 2022). Advanced age, cumulative chemotherapeutic exposures, and high-dose regimens further elevate the risk of nephrotoxicity (Donderski, et al., 2023). Additional contributing factors include dehydration, concomitant nephrotoxic medications, and impaired nutritional status, all of which may potentiate renal susceptibility (Ameer, 2022).

5. Pathogenesis

The pathogenesis of chemotherapy-induced nephrotoxicity primarily involves a cascade of oxidative stress, inflammatory activation, and apoptosis within tubular epithelial cells (Yoon, et al., 2022). Platinum compounds generate excessive reactive oxygen species (ROS), which promote oxidative injury to DNA, proteins, and membrane lipids of renal tubular cells (Donderski, et al., 2023). ROS accumulation disrupts mitochondrial membrane potential, reduces ATP production, and activates intrinsic apoptotic pathways (Yoon, et al., 2022). Cisplatin also induces renal vascular dysfunction, leading to reduced renal blood flow and localized ischemia that exacerbate tubular damage (Donderski, et al., 2023). Chemotherapy exposure upregulates pro-inflammatory cytokines such as TNF- α, IL-1β, and IL-6, amplifying tubular injury through immune-mediated mechanisms (Yoon, et al., 2022). Activated neutrophils and macrophages contribute to additional tissue injury through the release of proteolytic enzymes and the generation of oxidative bursts (Lima, et al., 2020). Structural injury to proximal and distal tubules triggers the rapid release of NGAL from tubular epithelial cells and activated neutrophils (Lima, et al., 2020). NGAL concentrations rise within hours of tubular insult, reflecting early cellular stress before measurable reductions in glomerular filtration occurs (Zhao, et al., 2021). This early increase in NGAL represents a protective compensatory response, attributed in part to its siderophore-binding capacity that limits iron-mediated oxidative injury (Lima, et al., 2020).

6. Clinical Manifestation

The clinical manifestations of chemotherapy-induced nephrotoxicity vary according to the extent and pattern of tubular and glomerular involvement (Yoon, et al., 2022). Early symptoms are frequently nonspecific, including malaise, anorexia, nausea, or subtle reductions in urine output (Yoon, et al., 2022). Laboratory findings commonly demonstrate rising serum creatinine levels and declining estimated glomerular filtration rate, indicating evolving renal dysfunction (Yoon, et al., 2022). Electrolyte disturbances particularly hypomagnesemia and hypokalemia are frequent consequences of impaired tubular reabsorption (Ameer, 2022). Cisplatin induced magnesium wasting may occur even prior to measurable changes in serum creatinine, reflecting early tubular dysfunction (Donderski, et al., 2023). Severe or rapidly progressive injury may culminate in acute kidney injury, characterized by

abrupt deterioration in renal function and increased risk of hospitalization or treatment interruption (Zhao, et al., 2021). Chronic or cumulative nephrotoxicity may present with persistent proteinuria, hypertension, or progressive decline in renal function consistent with chronic kidney (Ammirati, 2020). Because conventional biomarkers rise only after significant nephron loss, early tubular injury may remain clinically silent unless more sensitive biomarkers such as NGAL are employed (Lima, et al., 2020).

7. Diagnosis

The diagnosis of chemotherapy induced nephrotoxicity relies on the integration of clinical evaluation, laboratory testing, and detailed treatment history (Yoon, et al., 2022). Routine parameters such as serum creatinine, blood urea nitrogen, and estimated glomerular filtration rate remain widely used but lack adequate sensitivity for detecting early tubular injury (Yoon, et al., 2022). Because serum creatine rises only after substantial nephron loss, it may fail to identify subclinical or evolving renal damage in patients undergoing chemotherapy (Lima, et al., 2020). NGAL has emerged as a promising biomarker due to its rapid increase within 2-6 hours of tubular injury following exposure to nephrotoxic agents (Zhao, et al., 2021). Both serum and urinary NGAL measurements provide early evidence of subclinical tubular dysfunction prior to detectable changes in conventional markers (Lima, et al., 2020). Studies involving platinum-based regimens have demonstrated that NGAL elevation precedes serum creatinine rise, supporting its role in early detection of nephrotoxicity (Donderski, et al., 2023). Imaging modalities such as ultrasonography or CT scan are generally reserved for excluding obstructive or structural causes and are not routinely required for diagnosis of chemotherapy related renal injury (Yoon, et al., 2022). Differential diagnosis must consider alternative etiologies such as sepsis, dehydration, or concomitant administration of nephrotoxic medications (Ameer, 2022).

8. Management

Management of chemotherapy-induced nephrotoxicity focuses on prevention, early detection, and mitigation of further renal injury (Yoon, et al., 2022). Adequate hydration before and after chemotherapy is essential to reduce tubular exposure to nephrotoxic agents and enhance renal clearance (Ameer, 2022). Regular monitoring of renal function is recommended, particularly in patients receiving high risk agents such as cisplatin (Donderski, et al., 2023). Dose adjustment or temporary discontinuation of chemotherapy may be required when significant elevations in serum creatinine or reductions in estimated glomerular filtration rate occur (Yoon, et al., 2022). The incorporation of NGAL monitoring may allow earlier identification of tubular injury and facilitate timely interventions before irreversible damage develops (Lima, et al., 2020). Pharmacologic interventions remain limited, although antioxidant agents such as N-acetylcysteine have shown potential in reducing oxidative stress associated with nephrotoxicity (Ameer, 2022). Supportive measures, including electrolyte correction, nutritional optimization, and avoidance of additional nephrotoxic medications, play an essential role in mitigating further renal impairment (Ameer, 2022). In severe cases of acute kidney injury, renal replacement therapy may be required to stabilize metabolism and fluid disturbances (Yoon, et al., 2022).

9. Prognosis

The prognosis of chemotherapy-induced nephrotoxicity is influenced by the severity of renal injury, timeliness of detection, and adequacy of therapeutic interventions (Yoon, et al., 2022). Early identification of renal injury often results in partial or complete recovery of kidney function, particularly when chemotherapeutic regimens are promptly adjusted (Lima, et al., 2020). Delayed diagnosis or repeated exposure to nephrotoxic agents may lead to persistent renal impairment and progression toward chronic kidney disease (Ammirati, 2020). Elevated NGAL levels have been associated with worse renal outcomes, reflecting ongoing tubular stress and increased risk of developing overt renal dysfunction (Zhao, et al., 2021). A decline in NGAL concentrations following intervention may indicate tubular recovery and improvement in renal status (Lima, et al., 2020). Overall the incorporation of early biomarkers such as NGAL may improve long-term renal prognosis by enabling earlier detection of subclinical injury and guiding timely management (Donderski, et al., 2023).

10. Conclusion

Chemotherapy induced nephrotoxicity represents a significant clinical challenge in the management of breast cancer patients. Conventional renal biomarkers such as serum creatinine and estimated glomerular filtration rate lack sensitivity for the early detection of tubular injury, often delaying diagnosis until substantial renal impairment has occurred. NGAL has emerged as a highly sensitive and early marker of tubular damage, with levels rising hours after nephrotoxic exposure. Evidence from clinical and experimental studies demonstrates that NGAL elevation frequently precedes changes in serum creatinine, underscoring its value in detecting subclinical nephrotoxicity. Integration of NGAL monitoring into routine clinical practice may enhance early diagnosis, enable timely therapeutic intervention, and ultimately improve renal outcomes in patients receiving chemotherapy.

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