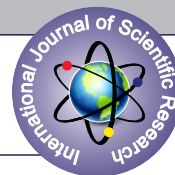


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PERSPICACIOUS EVALUATION OF THE ESCALATING INCIDENCE, MULTIFACETED ETIOLOGY, AND PROGNOSTIC IMPLICATIONS OF ACUTE KIDNEY INJURY AMONG CRITICALLY ILL ONCOLOGICAL PATIENTS WITHIN CONTEMPORARY INTENSIVE CARE ENVIRONMENTS



Clinical Science

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ABSTRACT

The burgeoning global burden of oncological pathologies, coupled with an augmented life expectancy among the afflicted, has precipitated a discernible escalation in intensive care unit (ICU) admissions, where cancer patients now constitute a staggering 15% of all hospitalizations. It is estimated that a quinquennial proportion of the oncological population is destined to encounter a critical exigency necessitating such specialized intervention, a trend fueled by the inexorable rise in cancer incidence worldwide. This demographic is particularly susceptible to the deleterious onset of acute kidney injury (AKI), a complication whose etiology is often a labyrinthine confluence of factors, ranging from the direct pathological manifestations of the malignancy itself to the iatrogenic consequences of sophisticated therapeutic regimens and various non-malignant extraneous variables. Consequently, the clinical landscape demands a perspicacious understanding of these multifaceted triggers to mitigate the perils faced by this precarious patient population.

KEYWORDS

Cancer patients account for 15% of all admissions to the intensive care unit (ICU) and 5% of cancer patients are estimated to experience a critical illness resulting in ICU admission [1, 2]. These frequencies are increasing considering the global burden of cancer, the rise in cancer incidence and the increased longevity of cancer patients. Many patients develop acute kidney injury (AKI), the causes of which may be directly related to the cancer, its associated therapies, or non-cancer related factors [3].

Epidemiology and Impact of AKI in the Patient with Cancer

Depending on the underlying malignancy, the 5-year risk of AKI in cancer patients may be as high as 50% [4]. During critical illness, 25 to 60% of patients with cancer develop AKI. When AKI occurs, it is associated with an increased risk of mortality and morbidity and limits therapeutic options for the underlying malignancy which translates into high rate of failure to achieve remission [5]. Last, although the outcome of cancer patients in ICU has dramatically improved over the last decades, similar improvements have not been seen in those who require kidney replacement therapy (KRT) [2, 6].

Malignancy Associated AKI

Although the main risk factors for AKI in the ICU setting are common to the general ICU population, several causes related to malignancy are relatively unique.

Among them, obstruction and infiltration are both frequent and underestimated causes of AKI in patients with solid tumors and hematological malignancies. AKI is common in patients with tumor lysis syndrome (TLS), (>80%) and in critically ill patients with myeloma (80–90%) [5]. Renal involvement due to myeloma can take many forms although cast-nephropathy is the main pattern encountered. Nearly all hematologic and solid-organ cancers have been associated with TLS but it is much more common with large, chemosensitive tumors that have a high proliferative rate, such as Burkitt's lymphoma and acute lymphoblastic leukemia (TLS criteria shown in supplementary Fig. 1) [7]. TLS occurs as a consequence of massive cell destruction, releasing intracellular compounds into the extracellular space and leading to hyperuricemia, hyperkalemia, hyperphosphatemia and hypocalcemia. Within the kidney, cytokine

release associated with acute tubular injury, acute uric acid nephropathy, and acute nephrocalcinosis may contribute to the development of AKI. The exact incidence depends on the type of malignancy, its proliferative rate and tumor burden along with patient related factors, including age, fluid status and presence of splenomegaly.

Drug and Therapy Associated AKI

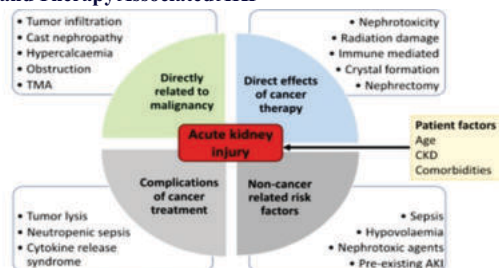


Fig. 1 Factors contributing to AKI in cancer patients. AKI acute kidney injury, CKD chronic kidney disease, TMA thrombotic microangiopathy

As the number of effective, but potentially nephrotoxic, chemotherapeutic regimens are released into clinical practice, oncologists, intensivists and consulting nephrologists should be familiar with their adverse renal effects [8]. Clinicians should also be well versed in the risk factors for AKI and preventive measures available for the various chemotherapy regimens, as well as effective treatment options for nephrotoxic consequences [9]. The different forms of AKI due to anti-cancer medications include all of the various anatomic and histologic sections of the kidney (Supplementary Fig. 2). In broad terms, AKI may be associated with more traditional cytotoxic chemotherapies such as platin-based drugs (cisplatin) as well as newer targeted therapies (such as tyrosine kinase inhibitors and drugs targeting the vascular endothelial growth factor pathway) and medications that harness the power of the immune system to kill tumor cells (such as immune checkpoint inhibitors and chimeric antigen-receptor T cells) [8, 10, 11].

While the majority of AKI associated with anti-cancer drugs is likely due to acute tubular injury, it is important to be familiar with the myriad of other toxicities that result in an acute fall in glomerular filtration rate

(GFR) (Supplementary Fig. 2). Of particular importance for the care of ICU patients is the rapid recognition of drug-induced thrombotic microangiopathies (TMA) (defined by the presence of hemolytic anemia, thrombocytopenia, organ dysfunction and normal coagulation) and immune checkpoint inhibitor associated acute interstitial nephritis. Both can be insidious and associated with other organ dysfunction and require a high degree of suspicion [10, 12]. Obviously, an individual patient's risk of chemotherapy associated AKI is impacted by concomitant medications, patient related factors, including reduced GFR, and usual risk factors for AKI during critical illness (Fig. 1 and supplementary Fig. 2).

Management

In many cases, the exact etiology of AKI may be uncertain or possibly multifactorial, including non-cancer related causes. This is especially true in ICU patients with concomitant sepsis. In unclear cases, and especially if treatable etiologies such as myeloma kidney are contemplated, a kidney biopsy should be considered. Concomitantly, all potentially nephrotoxic medications should be stopped if possible.

TLS can have life-threatening consequences, including hemodynamic instability, lysis pneumopathy and hyperkalemia. The management follows the same approaches as prophylaxis: intravenous hydration and correction of hypovolemia, avoidance of urine alkalization, and rapid and efficient control of hyperuricemia and hyperkalemia [7]. Rasburicase, a recombinant urate oxidase, is effective at converting uric acid to a more soluble form in both pediatric and adult patients but is contraindicated in the setting of glucose-6-phosphate dehydrogenase deficiency due to the risk of severe hemolysis. When medical management fails to control metabolic disturbances or hyperkalemia, urgent KRT should be considered.

Myeloma kidney prevention and management mainly rely on hydration and correction of predisposing factor. Urine alkalization, once advocated to increase solubility of light chains, remains recommended despite ongoing controversy. Bortezomib-based therapy for myeloma has been proven effective in allowing renal recovery in patients with cast-nephropathy. Attempts to remove light chains using plasma exchange or high cut-off membranes have led to disappointing results and are not recommended [13, 14].

In patients with immune checkpoint inhibitor associated AKI, early treatment with glucocorticoids is associated with better chances of kidney recovery [11]. However, data on dose and duration of glucocorticoid therapy are limited.

Management of TMA in patients with cancer is supportive. Potentially contributing drugs should be discontinued. There is no solid evidence supporting any particular therapeutic approaches and plasma exchange is usually ineffective.

The treatment of malignancy associated hypercalcemia consists of aggressive intravenous volume expansion with crystalloids and bisphosphonate therapy [15]. Adjunctive therapy may include calcitonin and corticosteroids.

Take-home Message

The genesis of Acute Kidney Injury (AKI) within the oncological landscape is rarely a singular misfortune; rather, it is a complex, multifactorial entanglement that demands both clinical vigilance and diagnostic precision. We find ourselves at a critical juncture where the imperative to preempt renal impairment is matched only by the necessity to disentangle its specific etiologies. Yet, we are currently hampered by a conspicuous paucity of definitive diagnostic benchmarks—a "gold standard" remains elusive, often forcing clinicians into the nebulous realm of empirical treatment, an approach that lacks the surgical specificity required for such high-stakes pathology.

Furthermore, the prognostic shadows cast by an episode of AKI are long and formidable. Beyond the immediate physiological insult, the subsequent recalibration—or outright abandonment—of chemotherapy regimens often compromises the primary therapeutic objective, particularly when renal restitution remains incomplete. To navigate this labyrinthine intersection of critical illness and malignancy, we must transcend traditional silos. What is required is a robust commitment to translational research and longitudinal inquiry, underscored by a multidisciplinary ethos. Only through a sophisticated, patient-centric prism can we hope to mitigate the

cascading adversities faced by those battling this dual burden.

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