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UNDERSTANDING THE DISEASE

Onco-nephrology: what the intensivist needs to know

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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] (Fig. 1).

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

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

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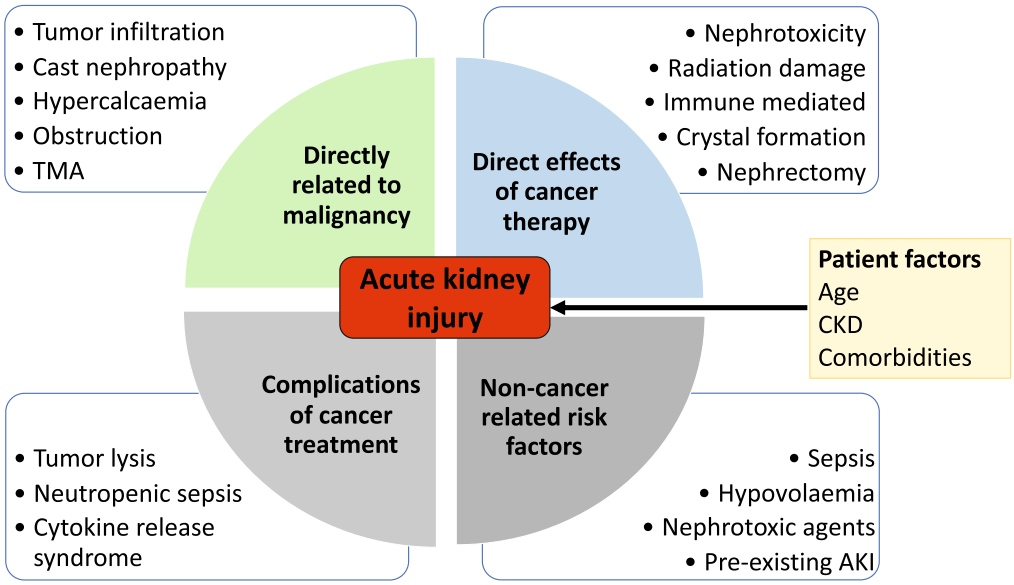

Fig. 1 Factors contributing to AKI in cancer patients. *AKI* acute kidney injury, *CKD* chronic kidney disease, *TMA* thrombotic microangiopathy

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 alkalinization, 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 alkalinization, 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

Malignancy associated AKI is often multifactorial. There is an urgent need to prevent AKI and to identify the specific underlying causes when AKI occurs to allow targeted therapy. The paucity of specific diagnostic tests is due in part to the lack of a "gold standard," where AKI patients are often treated empirically, irrespective of the cause. More diagnostic tools, translational studies with longitudinal biospecimen collection and intervention studies are urgently needed. Independent of the exact etiology of AKI, the prognosis of cancer patients is often significantly reduced following an episode of AKI. Changes to the chemotherapy treatment plan following an episode of AKI are likely to contribute, including in patients with incomplete renal recovery. Thus, the complex issues that arise in critically ill patients with underlying cancer require multidisciplinary care with a focus on patient-centered outcomes.

Supplementary Information

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Declarations

Conflicts of interest

MO reports no conflict of interest related to the content of the manuscript. MHR reports no conflict of interest. MD reports no conflict of interest related to the content of the manuscript. MD received consulting fees from Sanofi and Gilead-Kite, research support from Astute Medical and MSD, and speaker fees from MSD, Gilead-Kite and Astellas unrelated to manuscript scope.

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References

1. Azoulay E, Schellongowski P, Darmon M, Bauer PR, Benoit D, Depuydt P et al (2017) The Intensive Care Medicine research agenda on critically ill oncology and hematology patients. Intensive Care Med 43(9):1366–1382. https://doi.org/10.1007/s00134-017-4884-z
2. Ostermann M, Ferrando-Vivas P, Gore C, Power S, Harrison D (2017) Characteristics and outcome of cancer patients admitted to the ICU in England, Wales, and Northern Ireland and national trends between 1997 and 2013. Crit Care Med 45(10):1668–1676. https://doi.org/10.1097/ccm.0000000000002589
3. Seylanova N, Crichton S, Zhang J, Fisher R, Ostermann M (2020) Acute kidney injury in critically ill cancer patients is associated with mortality: a retrospective analysis. PLoS ONE 15(5):e0232370. https://doi.org/10.1371/journal.pone.0232370
4. Christiansen CF, Johansen MB, Langeberg WJ, Fryzek JP, Sørensen HT (2011) Incidence of acute kidney injury in cancer patients: a Danish population-based cohort study. Eur J Intern Med 22(4):399–406. https://doi.org/10.1016/j.ejim.2011.05.005
5. Darmon M, Vincent F, Canet E, Mokart D, Pène F, Kouatchet A et al (2015) Acute kidney injury in critically ill patients with haematological malignancies: results of a multicentre cohort study from the Groupe de Recherche en Réanimation Respiratoire en Onco-Hématologie. Nephrol Dial Transplant 30(12):2006–2013. https://doi.org/10.1093/ndt/gfv372
6. Darmon M, Bourmaud A, Georges Q, Soares M, Jeon K, Oeyen S et al (2019) Changes in critically ill cancer patients' short-term outcome over the last decades: results of systematic review with meta-analysis on individual data. Intensive Care Med 45(7):977–987. https://doi.org/10.1007/s00134-019-05653-7
7. Zafrani L, Canet E, Darmon M (2019) Understanding tumor lysis syndrome. Intensive Care Med 45(11):1608–1611. https://doi.org/10.1007/s00134-019-05768-x
8. Rosner MH, Perazella MA (2017) Acute kidney injury in patients with cancer. N Engl J Med 376(18):1770–1781. https://doi.org/10.1056/NEJMra1613984
9. Rosner MH, Jhaveri KD, McMahon BA, Perazella MA (2021) Onconephrology: the intersections between the kidney and cancer. CA Cancer J Clin 71(1):47–77. https://doi.org/10.3322/caac.21636
10. Gupta S, Short SAP, Sise ME, Prosek JM, Madhavan SM, Soler MJ et al (2021) Acute kidney injury in patients treated with immune checkpoint inhibitors. J Immunother Cancer. https://doi.org/10.1136/jitc-2021-003467
11. Gupta S, Gudsoorkar P, Jhaveri KD (2022) Acute kidney injury in critically ill patients with cancer. Clin J Am Soc Nephrol. https://doi.org/10.2215/cjn.15681221
12. Valério P, Barreto JP, Ferreira H, Chuva T, Paiva A, Costa JM (2021) Thrombotic microangiopathy in oncology—a review. Transl Oncol 14(7):101081. https://doi.org/10.1016/j.tranon.2021.101081
13. Hutchison CA, Cockwell P, Moroz V, Bradwell AR, Fifer L, Gillmore JD et al (2019) High cutoff versus high-flux haemodialysis for myeloma cast nephropathy in patients receiving bortezomib-based chemotherapy (EuLITE): a phase 2 randomised controlled trial. Lancet Haematol. 6(4):e217–e228. https://doi.org/10.1016/s2352-3026(19)30014-6
14. Bridoux F, Carron PL, Pegourie B, Alamartine E, Augeul-Meunier K, Karras A et al (2017) Effect of high-cutoff hemodialysis vs conventional hemodialysis on hemodialysis independence among patients with myeloma cast nephropathy: a randomized clinical trial. JAMA 318(21):2099–2110. https://doi.org/10.1001/jama.2017.17924
15. Rosner MH, Dalkin AC (2012) Onco-nephrology: the pathophysiology and treatment of malignancy-associated hypercalcemia. Clin J Am Soc Nephrol 7(10):1722–1729. https://doi.org/10.2215/cjn.02470312