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Acute kidney injury following cancer immunotherapy; collaboration of oncologists and nephrologists

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ABSTRACT

Acute kidney injury (AKI) is a known complication of cancer immunotherapy, which is a type of cancer treatment that uses the body's immune system to fight cancer cells. The mechanism of acute kidney injury (AKI) in cancer immunotherapy is thought to be related to the immune-mediated inflammation and cytokine release that can occur with immunotherapy. This inflammation can damage the kidney tubules and impair kidney function.

Keywords: Acute kidney injury, Cancer immunotherapy, Cancer cells, Kidney tubules, Cytokine release syndrome, Immune checkpoint inhibitors

Mini-Review

Implication for health policy/practice/research/medical education:
The mechanisms leading to acute kidney injury following cancer immunotherapy are due to the immune-mediated inflammation and injury to the kidneys.

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Introduction

Acute kidney injury (AKI) is a known side effect of cancer immunotherapy, including chimeric antigen receptor (CAR) T-cell therapy, immune checkpoint inhibitors, and other cancer immunotherapies (1). The causes of AKI in cancer immunotherapy recipients can vary depending on the specific type of therapy. For example, treatment with bispecific T cell-engaging antibodies and CAR T-cell can result in AKI as an outcome of tumor lysis syndrome, cytokine release syndrome (CRS), sepsis or particular CAR T-cell infiltration (1,2).

The immune checkpoint blockade commonly ensues in acute tubular interstitial nephritis (ATIN); however, glomerular involvement has also been explained (3). The incidence of AKI in cancer patients receiving immunotherapy varies depending on the type of immunotherapy used, ranging from 2% to 40% (4). The most commonly implicated immunotherapy drugs are anti-PD-1 antibodies like pembrolizumab and nivolumab and anti-CTLA-4 antibodies like ipilimumab (5).

Search strategy

For this review, we searched PubMed, Web of Science, EBSCO, Scopus, Google Scholar, Directory of Open Access Journals (DOAJ), and Embase, using different keywords including; acute kidney injury, cancer immunotherapy, cancer cells, kidney tubules, cytokine release syndrome and immune checkpoint inhibitors.

Long-term effects of AKI on cancer immunotherapy recipients

The long-term effects of acute kidney damage in cancer immunotherapy recipients can have significant implications for patient outcomes. The previous studies showed that AKI in cancer cases receiving immune checkpoint inhibitor agents was associated with increased mortality outcomes. The mortality risk at 60 days for patients with AKI was up to 67% compared to 10% for patients without AKI (3,6). Accordingly, the causes of AKI in cancer immunotherapy recipients can vary depending on the specific therapy. Treatment with bispecific T cell-engaging antibodies and CAR T cell may result in AKI as an outcome of CRS, tumor lysis syndrome, sepsis or specific CAR T-cell infiltration. In addition, immune checkpoint blockade frequently leads to ATIN. Nevertheless, glomerular diseases have also been detected (1,7).

Types of cancer immunotherapy across with AKI

CAR T-cell therapy can lead to AKI due to CRS or specific CAR T-cell infiltration (2). Moreover, bispecific T cell-engaging antibodies can cause acute kidney damage

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(8). Similarly, immune checkpoint inhibitors most often result in ATIN (3). Other cancer immunotherapies, such as bacillus Calmette-Guérin therapy, have also been associated with AKI (9).

Risk factors for developing AKI in cancer immunotherapy

Younger age has been identified as a risk factor for developing AKI in cancer immunotherapy recipients (9,10). Moreover, patients with lower baseline glomerular filtration rate are more susceptible to developing AKI during cancer immunotherapy (11). Different types of cancer immunotherapy have varying risks of causing AKI. For example, CAR T-cell therapy and immune checkpoint inhibitors have been related to a higher risk of AKI (12). Certain immunotherapies' specific mechanisms of action can contribute to the development of AKI. For example, bispecific T cell-engaging antibodies and CAR T- cell therapy can direct to AKI due to CRS (13).

AKI due to cytokine release syndrome

Cytokine release syndrome is a group of symptoms which can arise as an adverse effect of particular kinds of immunotherapy, mainly those that encompass T-cells. Cytokine release syndrome ensues when immune cells are triggered and release large amounts of cytokines into the circulation (14). Cytokines are small proteins that proceed as cell messengers to regulate the immune response. Nevertheless, high concentrations of cytokines may cause strengthened inflammation through the body, leading to CRS (15,16).

In the context of cancer immunotherapy, CRS can contribute to the development of AKI in recipients. Additionally, bispecific T cell-engaging antibodies and CAR T-cell therapy which are types of immunotherapies, can lead to AKI due to CRS (17,18). The excessive release of cytokines during CRS can cause widespread inflammation and damage to various organs, including the kidneys (19,20).

Role of macrophages in AKI due to cytokines release

Macrophages are immune cells that play a crucial role in the inflammatory response, both in AKI and chronic kidney disease (CKD). Macrophages can promote kidney repair or contribute to kidney damage, depending on their phenotype and the cytokine release (21,22). Among the cytokines released by macrophages, pro-inflammatory mediators such as interleukin-1 (IL-1), IL-6, and tumor necrosis factor (TNF) can contribute to kidney damage. Additionally, anti-inflammatory cytokines such as IL-10 and profibrotic factors like transforming growth factor-β (TGF-β) can also play a role in kidney damage (23,24). The role of M2 macrophages and related factors, such as CCL18, in AKI is still being studied. In the context of CRS-induced AKI in cancer immunotherapy recipients, macrophages and related cytokines can contribute to kidney damage (25). Macrophages can be activated by cytokines released from T-cells and other immune cells, which release pro-inflammatory cytokines and other mediators contributing to kidney damage (26). The exact role of macrophages in CRS-induced AKI is not fully understood, however their involvement in the inflammatory response and cytokine-mediated injury is believed to play a role (25). Direct renal cell toxicity is another probable mechanism of renal damage in CRS. The severity of CRS and its impact on the kidneys can vary among individuals and depend on factors such as the type of immunotherapy, the dose, and the patient's overall health (8). Close monitoring and early detection of AKI are important in managing and minimizing the risk of long-term complications in cancer immunotherapy recipients

Interaction of macrophages with kidney cells during renal inflammation

Under pathological conditions, kidney intrinsic cells and inflammatory cells in the renal tissue promote and restrain each other by several mechanisms, presenting an intricate and dynamic micro-environmental state that finally regulates cell fate decisions in the kidney. Macrophages can balance the progression of immune cell infiltration and inflammation in the kidney (27,28). Furthermore, intrinsic renal cells can interact with macrophages straightforwardly or through alterations in the tissue microenvironment. Macrophage depletion, modification, or polarization can affect the progression of AKI and the subsequent repair process (21,22). Macrophages can also promote fibrosis in the kidney by producing profibrotic factors such as TGF-β and interacting with other immune cells and intrinsic kidney cells (22,28). The specific mechanisms by which macrophages interact with intrinsic kidney cells during renal inflammation are still being studied. However, macrophages play a central role in the inflammatory reaction and tissue repair in the kidney (29,30). Understanding the complex interactions and signaling pathways involved in macrophage-intrinsic kidney cell crosstalk is important for developing targeted therapies to modulate their functions and promote kidney repair and regeneration (21,28).

Prognosis and treatment

The prognosis of AKI in cancer immunotherapy recipients depends on various factors, including the underlying cause, severity of renal damage, and timely intervention. Treatment options may include supportive care, discontinuation or modification of immunotherapy, and specific interventions targeting the underlying cause of AKI (1,31).

Management of AKI

AKI following cancer immunotherapy can be a serious complication that needs prompt evaluation and

management. It is an immune-related adverse event associated with the use of certain immunotherapy drugs, particularly immune checkpoint inhibitors. AKI management in the cancer immunotherapy setting involves several aspects (1,32). In mild cases, close monitoring of kidney function with hydration and cessation of the immunotherapy drug may be sufficient. However, in more severe cases, additional interventions such as high-dose corticosteroids or other immunosuppressive agents may be needed (4,33).

Conclusion

Prompt recognition and management of AKI following cancer immunotherapy is crucial to prevent further kidney damage and optimize patient outcomes.

Authors' contribution

Conceptualization: Sousan Mohammadi Kebar, Saeed Hoseininia.
Data curation: Sousan Mohammadi Kebar, Saeed Hoseininia.
Investigation: Sousan Mohammadi Kebar, Saeed Hoseininia.
Resources: Sousan Mohammadi Kebar, Saeed Hoseininia.
Supervision: Sousan Mohammadi Kebar.
Validation: Sousan Mohammadi Kebar, Saeed Hoseininia.
Visualization: Sousan Mohammadi Kebar.
Writing–original draft: Sousan Mohammadi Kebar, Saeed Hoseininia.
Writing–review and editing: Sousan Mohammadi Kebar, Saeed Hoseininia.

Conflicts of interest

The authors declare that they have no competing interests.

Declaration of generative AI and AI-assisted tools in the writing processes

During the preparation of this work, the authors utilized ChatGPT—a chatbot developed by OpenAI— to refine grammar points and language style in writing. Subsequently, the authors thoroughly reviewed and edited the content as necessary, assuming full responsibility for the publication's content.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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