Serious Kidney Injuries May Be Related to Cancer Therapies

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– Abhijat Kitchlu, MD, MSc

It is widely recognized that patients with cancer are at an increased risk of developing acute kidney injury (AKI) while undergoing cancer therapies, but to date, only small single-center studies have investigated the incidence of and risk factors for AKIs. However, a recent large-scale, population-based study (J Natl Cancer Inst. Published online November 13, 2018. doi:10.1093/jnci/djy167) reports that although approximately 1 in 10 patients with cancer who receive systemic therapy experience AKIs that result in hospitalization or require acute dialysis, AKIs also may occur in patients with a wider array of cancers than previously suspected. The 5-year cumulative incidence of AKI overall for all types of cancer combined was 7.8%.

Previous studies that investigated kidney dysfunction in patients with cancer focused on a few individual cancer types, such as kidney cancers, in which there is an obvious direct impact of treatment on kidney function, says lead study author Abhijat Kitchlu, MD, MSc. Dr. Kitchlu is a staff nephrologist and assistant professor in the division of nephrology in the department of medicine at the University of Toronto in Toronto, Ontario, Canada. To his knowledge, he says, this is the first large-scale, population-based study of a broad range of cancers and risk factors, both from the disease as well as the therapies, for developing kidney dysfunction while receiving cancer treatment. “This is an important issue with big implications for cancer patients,” says Dr. Kitchlu. “It affects when they can get their therapy, and even if they are eligible for some therapies. When we were developing this study, we were surprised to see what little data was out there regarding this issue.” This is especially true, he notes, for new therapies.

Study Details

The population-based cohort study included patients residing in Ontario, Canada, who were included in the Ontario Cancer Registry. All patients were eligible for single-payer, publicly funded health care under the Ontario Health Insurance Plan, thereby permitting access to administrative data such as billing for dialysis. The primary outcome was the time to either first hospitalization with an AKI or receipt of acute dialysis.

Among the 163,071 patients in the Ontario Cancer Registry who had received systemic cancer therapy between April 1, 2007, and March 31, 2014, the researchers found that 10,880 patients were hospitalized with serious AKIs or underwent acute dialysis. The incidence among patients who initiated systemic therapy for any cancer was 27 cases of AKI per 1000 person-years. Age and sex were found to have only minimal effects on the risks of AKI, but patients with more advanced cancer at the time of diagnosis were more vulnerable to developing an AKI.

The researchers were able to determine cancer stage for approximately 71.4% of patients. In the entire cohort, approximately 19.3% had stage IV cancer. In terms of cancer type, approximately 23.4% of patients had breast cancer, 13.2% had colorectal cancer, 12.7% had lung cancer, 6.3% had non-Hodgkin lymphoma, and 4.7% had prostate cancer. The most common comorbidities in this cohort included hypertension (41.2%), diabetes mellitus (20%), coronary artery disease (14.3%), and preexisting chronic kidney disease (4%).

The types of cancers among the patients were strongly related to their risk of AKI; among patients with common cancers, the highest 5-year cumulative AKI incidence was noted among those with multiple myeloma (26.0%), bladder cancer (19.0%), leukemia (15.4%), and kidney cancer (13.9%). The lowest incidence was observed among patients with

KEY POINTS

- AKI results from a variety of cancers and/or the administered therapy.
- Patients with multiple myeloma, bladder cancer, and cervical cancer appear to have the highest rates of AKI.
- In the current study, patients were more than twice as likely to develop an AKI within the first 90 days of their cancer treatment than afterward.
breast cancer (3.1%) and Hodgkin lymphoma (4.3%). In adjusted analyses including covariates such as demographics (age, sex, and income quintile), comorbidities (including diabetes, hypertension, heart disease, etc), cancer type and/or stage, and year of the initiation of systemic therapy, patients with multiple myeloma, bladder cancer, and cervical cancer had the highest hazard ratios (HRs) for AKI. Nephrotoxicities of the commonly used cytotoxic agents are believed to be a factor for all 3 of these cancers. In addition, paraprotein-related tubular and glomerular disease and hypercalcemia are risk factors in patients with multiple myeloma, and urinary obstruction is thought to contribute to AKIs in individuals with cancers of the bladder or cervix.

Among patients with common comorbidities, those most strongly associated with AKI included chronic kidney disease, a previous AKI, diabetes mellitus, congestive heart failure, and HIV/AIDS, with HRs of 1.8, 1.69, 1.43, 1.36, and 1.36, respectively, noted in adjusted models including age, sex, income quintile, cancer type and/or stage, and year of initiation of systemic therapy compared with patients without these comorbidities. According to the researchers, the highest risk of AKI occurred during the initial 90 days after the initiation of systemic therapy.

One surprise, says Dr. Kitchlu, is that older patients were taking other drugs when they initiated their cancer therapies, which increased the risk of AKI by 20% to 30%. For example, approximately 51.3% of the patients were taking angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. Others had been prescribed beta blockers (28.7%), calcium channel blockers (27.1%), diuretics (29.1%), nonsteroidal anti-inflammatory drugs (15.2%), and statins (45.4%).

Patients who were administered angiotensin-converting enzyme inhibitors or angiotensin receptor blockers at the time of systemic therapy had the greatest risk of developing an AKI (adjusted HR, 1.30), followed by patients who were prescribed diuretics (adjusted HR, 1.20) or calcium channel blockers (adjusted HR, 1.18). Beta blockers were found to slightly increase risk (adjusted HR, 1.10), whereas statins did not appear to present a significantly increased risk of AKI.

The researchers speculate that the association between these drugs and AKI may stem from the increased risk of hemodynamic and/or prerenal stress on the kidneys when patients are hypovolemic as a result of the side effects of cancer therapy (eg, with emetogenic chemotherapy). Dr. Kitchlu says withdrawing these medications when initiating cancer treatment should be investigated for certain patients.

“It is critically important to define the risk settings for AKI, and this study provides critical information,” says Mitchell Rosner, MD, the Henry Mulholland Professor of Medicine and chair of the department of medicine at the University of Virginia in Charlottesville, Virginia.

According to Dr. Rosner, one of the most important findings is the rising incidence of AKI in patients with cancer. “This may be due to increased age, comorbid conditions—especially chronic kidney disease—as well as newer chemotherapeutic agents that increase nephrotoxicity.”

Developing strategies that prevent AKI, he says, is imperative. “This study helps us outline risks for AKI, and sets the stage for more accurate risk profiling,” Dr. Rosner says. “My hope is that oncologists will carefully assess kidney function and monitor patients closely for AKI. In those at high risk for AKI, the development of multidisciplinary teams to manage and mitigate risk would be critical. [Oncology] clinicians should get nephrologists involved early in these situations.”

Dr. Kitchlu agrees. “I certainly see in my practice a growing need for close, multidisciplinary involvement in cancer care. We’ve even coined our clinic an ‘onco-nephrology clinic,’” he says. “I think, moving forward, there’s going to be a need for more interaction between cancer specialists, both researchers and clinical specialists focused on other organ systems, such as the heart and the kidney.”

Another vital step, Dr. Rosner adds, will be to develop risk prediction scoring systems as well as novel biomarkers to detect and predict the risk of AKI in patients with cancer. “In addition, we need to understand mechanisms of nephrotoxicity and develop strategies to protect the kidney,” he says.

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