Onconephrology: Renal Disorders in Patients with Solid Malignancies

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Abstract

Background: Onconephrology is an emerging subspecialty addressing the complex, bidirectional relationship between kidney disease and cancer. Patients with solid malignancies frequently develop acute kidney injury or carry pre-existing chronic kidney disease, both of which worsen oncological outcomes and complicate therapeutic decisions. The kidneys serve as the primary route of drug elimination, rendering them uniquely vulnerable to chemotherapeutic, targeted, and immunological agents. Understanding the spectrum of renal disorders in this population is essential for optimising cancer treatment, adjusting drug dosing, and improving patient survival.

Keywords: Onconephrology; acute kidney injury; chronic kidney disease; solid malignancies; nephrotoxicity; immune checkpoint inhibitors; renal cell carcinoma; glomerulonephritis

Introduction

Onconephrology is a new subspecialty of nephrology that recognises the important intersections of kidney disease with cancer. This intersection takes many forms and includes drug-induced nephrotoxicity, electrolyte disorders, paraneoplastic glomerulonephritis, and the interactions of chronic kidney disease with cancer treatment and prognosis. Broadly, the mission of onconephrology is to help cancer teams identify, treat, and, where possible, prevent kidney problems in their patients (1).

Recently, onconephrology has become a recognised field that necessitates ongoing communication and collaboration between nephrologists and oncologists, given that renal complications can directly determine whether a patient can continue receiving life-prolonging therapy (2).

The kidneys are the main site of drug elimination from the body and are consequently exposed to high concentrations of chemotherapeutics, along with their active and inactive metabolites, which frequently leads to nephrotoxicity. They also serve as a major excretory route for metabolites released from cancer cells destroyed by treatment, most notably uric acid in tumour lysis syndrome (3). Cancer itself can damage the kidneys through urinary tract obstruction, direct renal infiltration, glomerular injury from paraprotein deposition, and metabolic derangements such as hypercalcaemia (4).

At the same time, pre-existing chronic kidney disease limits treatment options, complicates drug dosing, restricts access to clinical trials, and independently worsens cancer-related mortality (5).

Prevalence of Chronic Kidney Disease in Cancer Patients

Chronic kidney disease may preexist in a substantial proportion of patients presenting with cancer, largely because of shared comorbid conditions such as diabetes mellitus and hypertension, which are highly prevalent in the population most affected by malignancy. Two observational studies demonstrated that nearly 50% of patients with cancer had an estimated glomerular filtration rate below 90 mL/minute/1.73 m², while the prevalence of stage 3 chronic kidney disease was 12% and fewer than 1% had stage 4 disease (6).

A further study of 4,077 patients with cancer found that 30% had an eGFR below 60 mL/minute/1.73 m², and 8.3% had an eGFR below 45 mL/minute/1.73 m², a level at which clinically significant consequences for drug dosing and treatment eligibility become inevitable (***5***).

Across multiple tumour types, only a minority of patients begin systemic therapy with fully preserved kidney function. Only 38.6% of patients with breast cancer, 38.9% of those with lung cancer, and 38.3% of those with prostate cancer had a GFR at or above 90 mL/minute/1.73 m² at the initiation of treatment (5). Overall, chronic kidney disease defined as an eGFR below 60 mL/minute/1.73 m² has a prevalence ranging from 12% to 25% across major cancer populations (7).

An age-calibrated perspective is important in interpreting these figures, since the physiological decline in GFR with ageing can confound the definition of true intrinsic kidney disease, though individuals with an eGFR below 45 mL/minute/1.73 m² almost certainly have clinically significant disease irrespective of age (8).

Chronic kidney disease in patients who have cancer is associated with a 12% to 27% higher risk of death compared with cancer patients who have preserved renal function, with cancer-specific mortality rising sharply as eGFR falls below 30 mL/minute/1.73 m² (9).

Acute Kidney Injury in Cancer Patients

Acute kidney injury is a common and serious occurrence in patients with cancer. In a Danish population-based study of 37,267 patients with incident cancer, 27% developed acute kidney injury over five years, and 7.6% developed severe injury requiring dialysis support, with the highest rates seen in patients with kidney cancer, liver cancer, and multiple myeloma. A more recent analysis of over 163,000 patients receiving cancer therapy found that dialysis-requiring acute kidney injury occurred in nearly 10% of all patients, with the highest incidence in multiple myeloma, bladder cancer, kidney cancer, and acute leukaemia (10).

Advanced cancer stage, pre-existing chronic kidney disease, and diabetes were all associated with an increased risk of acute kidney injury, and the annual incidence rose from 18 to 52 cases per 1,000 person-years over the study period, a rise largely attributed to increasing drug-related nephrotoxicities (11).

In intensive care settings, the burden of acute kidney injury is even heavier. A French study of patients admitted to intensive care with solid organ malignancy found that KDIGO stage 3 acute kidney injury occurred in 28% of patients, with a 42% mortality rate in this subgroup, while the overall acute kidney injury rate was 59% and 90-day mortality reached 37% (12).

The most common aetiologies were sepsis, hypovolaemia, urinary tract obstruction, tumour lysis syndrome, and hypercalcaemia. Outcomes are particularly poor in those requiring renal replacement therapy; a Brazilian intensive care study reported a hospital mortality rate of 87% in cancer patients with dialysis-dependent acute kidney injury, compared with 14% in those without acute kidney injury (13).

Cancer as a Cause of Renal Disease

Cancer can increase the likelihood of acute kidney injury through several distinct mechanisms. These include urinary tract obstruction from prostate cancer, urothelial cancer, gynaecological cancers, or retroperitoneal lymphadenopathy; direct infiltration of the kidney by renal carcinoma or lymphoma; glomerular injury from light-chain deposition disease; tubular injury from cast nephropathy; and metabolic derangement from hypercalcaemia. Paraneoplastic glomerulopathies are also well recognised and encompass membranous nephropathy, IgA nephropathy, minimal change disease, membranoproliferative glomerulonephritis, and extracapillary glomerulonephritis, each potentially arising from tumour antigen-driven immune complex formation (14).

Malignant ureteral obstruction is a particularly important cause of chronic kidney disease in cancer patients, with the most common culprits being cervical, bladder, and prostate cancers, as well as retroperitoneal fibrosis secondary to radiotherapy. The prevalence of chronic kidney disease is notably high in patients with kidney cancer at 29% and bladder cancer at 46%, often predating surgical intervention. In kidney transplant recipients, the incidence of cancer is even higher than in patients with chronic kidney disease alone, with Kaposi's sarcoma and skin cancer accounting for 75% of cases, while solid tumours of the liver, kidney, and lung are also frequently encountered, attributable in part to inflammatory microenvironments, oncogenic viral infections, and long-term immunosuppressive therapy (15).

Nephrotoxicity of Conventional Cytotoxic Agents

Systemic anticancer treatment can damage the kidney directly or indirectly. Nephrotoxicity is a serious adverse drug reaction of conventional cytotoxic agents that can affect both the efficacy of cancer treatment and patient survival. Cisplatin, one of the most widely used chemotherapy agents across a broad range of cancers, causes acute kidney injury in 20% to 30% of cases. Its nephrotoxic mechanism involves accumulation in the S3 segment of the proximal tubule, where it promotes glutathione depletion and generates excessive mitochondrial reactive oxygen species, leading to cellular oxidative stress and tubular necrosis. Strategies under investigation to reduce cisplatin nephrotoxicity include sodium thiosulfate in paediatric patients, DPP4 inhibitors such as teneligliptin, and honokiol, a natural compound derived from magnolia bark that activates SIRT3 and confers anti-inflammatory and nephroprotective effects (16, 17).

Ifosfamide exerts its nephrotoxic effects primarily through its metabolites rather than the parent drug, with chloroacetaldehyde and isophosphoramide mustard contributing to proximal tubulopathy and acute tubular necrosis, while acrolein is linked to haemorrhagic cystitis. Methotrexate, used in osteosarcoma and haematological malignancies, can cause crystal nephropathy, and glucarpidase, a bacterial enzyme, is available to reduce serum methotrexate concentrations in patients with impaired renal clearance (18).

Gemcitabine therapy has been associated with thrombotic microangiopathy, a rare but serious complication for which eculizumab, a C5 complement inhibitor, has been used with some success (19).

Bevacizumab causes nephrotic-range proteinuria through structural damage to the glomerular filtration barrier in 1% to 2% of patients, reflecting the central role of VEGF in maintaining podocyte integrity (19).

Nephrotoxicity of Targeted Agents

Targeted agents have expanded the oncological armamentarium considerably, but their renal side effects are numerous and clinically significant. Anti-VEGF agents such as bevacizumab, pazopanib, and sunitinib can cause thrombotic microangiopathy, arterial hypertension, and proteinuria, reflecting the physiological importance of VEGF in maintaining the integrity of glomerular endothelium, mesangium, and peritubular capillaries (20).

Anti-EGFR monoclonal antibodies, including cetuximab and panitumumab, are associated with hypomagnesaemia due to increased urinary magnesium wasting, as EGFR on the basolateral membrane of the distal tubule is integral to magnesium reabsorption (21).

Anti-HER2 agents such as trastuzumab and pertuzumab may cause indirect nephrotoxicity through cardiotoxicity and the resulting cardiorenal syndrome (22).

BRAF inhibitors, particularly vemurafenib, can induce acute allergic interstitial nephritis, acute tubular necrosis, and Fanconi syndrome with associated electrolyte disturbances including hypophosphataemia, hyponatraemia, and hypokalaemia (23).

ALK inhibitors such as crizotinib have been linked to hypophosphataemia, reduced GFR, proteinuria, and haematuria, typically within the first two weeks of treatment, while ibrutinib, a BTK inhibitor used in chronic lymphocytic leukaemia, is also associated with acute kidney injury (24).

Carfilzomib, a proteasome inhibitor used in multiple myeloma, can cause thrombotic microangiopathy and podocytopathy presenting as acute kidney injury, and rituximab may cause electrolyte disturbances and acute kidney injury particularly when tumour burden is high (25).

Nephrotoxicity of Immunotherapy

Older immunotherapeutic agents have well-characterised renal toxicity profiles. Recombinant interleukin-2 causes capillary leak syndrome with hypovolaemia and prerenal acute renal failure, while recombinant interferon-alpha can induce proteinuria, nephrotic syndrome, thrombotic microangiopathy, and glomerular diseases including minimal change disease and focal segmental glomerulosclerosis (26).

Immune checkpoint inhibitors targeting PD-1, PD-L1, and CTLA-4 have transformed oncology but carry well-documented renal risks. Treatment with pembrolizumab causes acute interstitial nephritis leading to renal failure in approximately 2% of patients, while nivolumab can cause hypophosphataemia, proteinuria, and hypertension. Ipilimumab is associated with nephrotic syndrome, acute tubular necrosis, acute interstitial nephritis, and acute kidney injury, some cases of which respond to corticosteroids (27). The combination of anti-CTLA-4 and anti-PD-1 therapy carries a higher risk of acute kidney injury than either agent alone, with incidences reaching up to 5% with combined use . In a single-centre study of 826 patients with solid organ malignancies treated with checkpoint inhibitors, 15% developed acute kidney injury, with the main presentation being subnephrotic-range proteinuria and eosinophiluria consistent with acute interstitial nephritis on biopsy (28).

The exact mechanism by which checkpoint blockade triggers acute interstitial nephritis remains incompletely understood, though it is likely mediated by loss of immune tolerance affecting tubular antigens. Management depends on severity and includes drug discontinuation with or without systemic corticosteroids; nonsteroidal alternatives such as mycophenolate mofetil and rituximab are reserved for steroid-refractory cases (29).

CAR T-Cell Therapy and Renal Complications

CAR T-cell therapy has opened new therapeutic possibilities for haematological malignancies and is under investigation in solid tumours including pancreatic cancer. The therapy is associated with cytokine release syndrome, which comprises systemic inflammation, cardiomyopathy, and acute kidney injury driven by the release of interleukins 1, 6, and 8 (30).

The acute kidney injury seen in this context is multifactorial and usually reversible, with the most important cause being haemodynamic compromise from cytokine-mediated vasodilation, which reduces renal perfusion and cardiac output. In one study of 78 adults with diffuse large B-cell lymphoma receiving CAR T-cell therapy, 85% developed cytokine release syndrome and 19% were diagnosed with acute kidney injury, while electrolyte disturbances including hypophosphataemia (75%), hypokalaemia (56%), and hyponatraemia (51%) were widespread (31). Preventive and therapeutic strategies include corticosteroids, vasopressor su

pport, and tocilizumab, an anti-IL-6 monoclonal antibody approved by the FDA, which mitigates the inflammatory cascade driving the syndrome (32).

Assessment of Kidney Function in Cancer Patients

Precise GFR measurement is essential in patients with cancer to determine optimal drug dosing, monitor kidney function, and inform prognosis. Unfortunately, all available formulae can under- or overestimate GFR, and the presence of sarcopenia, which is common in cancer patients with cachexia, leads to reduced serum creatinine and consequent overestimation of GFR (33).

Different creatinine-based equations are used in clinical practice, including the Cockcroft-Gault formula, the MDRD equation, and the CKD-EPI equation, though these were developed predominantly in non-cancer populations and their accuracy in oncological settings is uncertain (34). A large study demonstrated that the CKD-EPI equation adjusted for body surface area was the most accurate and least biased estimator of GFR in patients with cancer when compared against radioisotopic clearance with chromium-51 EDTA (34).

The conference workgroup convened for the KDIGO Controversies Conference agreed that the CKD-EPI equation is the current best approach for dosing chemotherapeutic agents in patients with chronic kidney disease (35). Cystatin C-based equations may offer better accuracy for predicting drug elimination by the kidneys; however, cathepsin D-mediated proteolysis in cancer patients may lower cystatin C independently of renal function, making universal adoption of cystatin C equations

inadvisable without further validation (35).

Kidney Disease and Solid Organ Cancer

Nephrectomy, the primary surgical treatment for kidney cancer, is an independent risk factor for subsequent kidney injury. After radical nephrectomy, the reduction in renal mass leads to a fall in GFR, particularly in patients with pre-existing kidney disease, and the remaining nephrons are susceptible to hyperfiltration injury (36).

The risk of reaching an eGFR below 60 mL/minute/1.73 m² is significantly higher after radical nephrectomy than after partial nephrectomy (58.7% vs. 38.4%), which has strengthened the case for nephron-sparing approaches where technically feasible. Current guidelines recommend partial nephrectomy for T1 tumours confined to the kidney and smaller than 7 cm, with consideration for selected T2 and T3a cases, while cytoreductive nephrectomy in metastatic disease is now generally preceded by systemic therapy based on the results of the CARMENA and SURTIME trials (37).

Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers should be considered in nephrectomised patients with chronic kidney disease when there are clinical indications such as hypertension, proteinuria, or cardiac disease. Meta-analyses of RAS inhibition in cancer patients have suggested a 40% reduction in cancer recurrence risk and a 25% reduction in mortality risk, with particular benefit in urinary tract malignancies including renal cell carcinoma, upper tract urothelial cancer, and bladder cancer (38).

Contrast-induced acute kidney injury is a relevant concern in cancer patients undergoing repeated CT scanning, especially those with eGFR below 60 mL/minute/1.73 m², though recent propensity score-matched analyses encompassing more than 60,000 patients have questioned whether contrast-enhanced CT significantly raises acute kidney injury risk above that of unenhanced imaging. An exaggerated fear of contrast nephropathy should not lead to withholding diagnostically necessary imaging, and in patients with CKD stages 4 to 5, reducing contrast dose and using iso-osmolar media are preferable to denying the scan altogether (39).

Conclusion

The intersection of kidney disease and solid malignancy is clinically intricate and consequential. Chronic kidney disease and acute kidney injury are both common in cancer patients, arising from the tumour itself, its metabolic effects, surgical interventions, and the expanding repertoire of nephrotoxic treatments including cytotoxic chemotherapy, targeted agents, immunotherapies, and CAR T-cell therapy. Renal impairment in turn limits treatment options, reduces drug efficacy, complicates dosing, and worsens survival. Addressing this intersection requires close collaboration between oncologists and nephrologists, accurate and appropriate assessment of renal function, careful attention to preventive strategies, and a willingness to individualise treatment decisions based on a patient's full clinical picture (39).

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