The link between kidney disease and cancer: complications and treatment

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Acute and chronic kidney disease encompasses a complex set of diseases that can both lead to, and result from, cancer. In particular, kidney disease can arise from the use of chemotherapeutic agents. Many of the current and newly developed cancer chemotherapeutic agents are nephrotoxic and can promote kidney dysfunction, which frequently manifests during the terminal stages of cancer. Given the link between kidney disease and cancer development and treatment, the aim of this Review is to highlight the importance of multidisciplinary collaboration between oncologists and nephrologists to predict and prevent chemotherapeutic-induced nephrotoxicity. As new therapies are introduced to treat cancer, new renal toxicities require proper diagnosis and management. We anticipate that multidisciplinary collaborations will lead to the development and implementation of guidelines for clinicians to improve the therapeutic management of patients with both cancer and renal impairment.

Lancet 2020; 396: 277–87

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Introduction

Cancer is the second leading cause of death worldwide.[1] The WHO's International Agency for Research on Cancer estimates that the global incidence of newly diagnosed cancer reached 18·1 million in 2018 and that 9·6 million people died of cancer during the same period.[1] Over the past 25 years the diagnosis, management, and treatment of cancer has changed considerably. A key component underlying this evolution is the shift from the reliance on gross examination and histological analysis of a tumour to molecular genotyping and molecular diagnostics. Advancements in cancer prevention include the improved recognition of predisposing factors and enhanced public health efforts. In addition, improvements in our understanding of the molecular biology and immunology of tumours and their microenvironments has led to an increase in targeted drug discovery. Likewise, advancements in minimally invasive surgery, together with progress in imaging and refinements in radiotherapy, are improving patient survival and reducing the rates of hospitalisation. Most patients with cancer are treated in an outpatient setting. These developments are benefiting patients with earlier stages of the disease, as well as patients with advanced or metastatic cancer who experience a longer and better quality of life. Thus, cancer has now become a chronic disease.[2]

Despite these advances, cancer, and the therapeutic agents used for treatment, exact a considerable toll on the major organ systems, including the heart (ie, cardiotoxicity), lungs (ie, pulmonary fibrosis), and bone (ie, bone marrow suppression), along with the risk of secondary tumours throughout the body. An increased incidence of acute kidney injury and chronic kidney disease among patients with cancer is of particular concern, especially in individuals with prostate, breast, lung, colorectal, or gynaecological cancers. The combination of cancer with impaired renal function worsens patients' outcomes and complicates their management and treatment.

The kidneys are the main site of drug elimination from the body and, consequently, these organs are exposed to high concentrations of chemotherapeutics, along with the drugs active and inactive metabolites, which can often lead to nephrotoxicity. The kidneys also serve as a major route of excretion for metabolites, including metabolites that are released from cancer cells destroyed by the treatment (ie, uric acid in tumour lysis syndrome).[3] For these reasons, drug concentrations and dosing are adjusted in patients with impaired renal function to reduce toxicity, especially for small molecules used in chemotherapy, hormones, and growth factors.[3]

Cancer therapy can have both a negative and positive impact on patient outcome because of the adverse effects on renal function. Kidney diseases in patients with cancer are associated with higher morbidity and mortality; in particular, for patients requiring renal replacement therapy because of acute kidney injury. This Review is intended to present a spectrum of renal problems and the complications of oncological treatments, including chimeric antigen receptor (CAR) T-cell therapy with unmet needs and future research into cancer treatment and management.

Kidney diseases in patients with cancer

Acute kidney injury

Cancer can increase the likelihood of acute kidney injury. This outcome is most likely a consequence of urinary tract obstruction (ie, prostate or urothelial cancer, cancer of the uterus or ovary, compression of the urinary tract by retroperitoneal node enlargement, a tumour mass, or retroperitoneal fibrosis); infiltration of the kidney (ie, renal cancer or lymphoma), glomerular (ie, light-chain deposition disease), or tubular (ie, cast nephropathy); or from hypercalcaemia (table 1). The kidneys might also be injured by chemotherapeutic agents due to thrombotic microangiopathy (eg, VEGF inhibitors such as bevacizumab, pazopanib, and sunitinib, immune checkpoint inhibitors such as ipilimumab and nivolumab, and antimetabolites, including gemcitabine), interstitial nephritis (eg, immune checkpoint inhibitors), or tubular damage (eg, cisplatin, methotrexate, trabectedin, or pemetrexed).

	Indication
Minimal change disease	Lung cancer, colon cancer, pancreatic cancer, bladder cancer, renal cell carcinoma, ovarian cancer, mesothelioma, non-melanoma skin cancer, thymoma, Hodgkin lymphoma, non-Hodgkin lymphoma, chronic lymphocytic leukaemia, chronic myeloid leukaemia, and myeloma
Membranoproliferative glomerulonephritis	Lung cancer, renal cell carcinoma, breast cancer, oesophageal cancer, gastric cancer, Wilms tumour, melanoma, non-melanoma skin cancer, thymoma, Hodgkin lymphoma, non-Hodgkin lymphoma, chronic lymphocytic leukaemia, chronic myeloid leukaemia, monoclonal gammopathy of undetermined significance, and myeloma
Mesangioproliferative glomerulonephritis	Lung cancer, renal cell carcinoma, non-melanoma skin cancer, gastric cancer, pancreatic cancer, liver cancer, and myeloma
IgA nephropathy	Lung cancer, pancreatic cancer, renal cell carcinoma, head and neck cancer, tongue cancer, Hodgkin lymphoma, and non-Hodgkin lymphoma
Focal segmental glomerulosclerosis	Lung cancer, renal cell carcinoma, breast cancer, oesophageal cancer, thymoma, Hodgkin lymphoma, non-Hodgkin lymphoma, chronic lymphocytic leukaemia, acute myeloid leukaemia, T-cell leukaemia, and myeloma
Membranous nephropathy	Lung cancer, colon cancer, pancreatic cancer, stomach cancer, prostate cancer, breast cancer, head and neck cancer, Wilms tumour, teratoma, ovarian cancer, cervical cancer, endometrial cancer, melanoma, non-melanoma skin cancer, pheochromocytoma, Hodgkin lymphoma, non-Hodgkin lymphoma, chronic lymphocytic leukaemia, acute myeloid leukaemia, and chronic lymphocytic leukaemia
Crescentic glomerulonephritis	Lung cancer, colon cancer, renal cell carcinoma, prostate cancer, gastric cancer, non-melanoma skin cancer, thymoma, Hodgkin lymphoma, and chronic lymphocytic leukaemia
Thrombotic microangiopathy	Lung cancer, breast cancer, and gastric cancer
Amyloid A amyloidosis	Renal cell carcinoma, gastrointestinal stromal tumour, spleen sarcoma, and Hodgkin lymphoma
Anti-glomerular basement membrane glomerulonephritis	Hodgkin lymphoma
ANCA-associated vasculitis	Prostate cancer, bladder cancer, non-Hodgkin lymphoma, leukaemia, non-melanoma skin cancer, and lung cancer

ANCA=antineutrophil cytoplasmic antibody.

Table 1: **Paraneoplastic glomerulopathies in cancer patients**

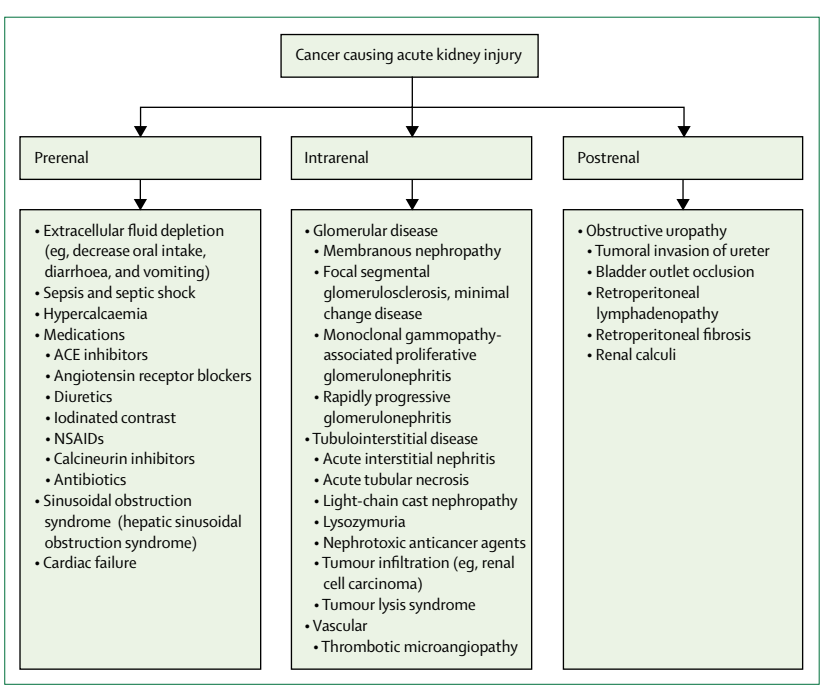

Figure 1: **Causes of acute kidney injury in malignancy**
ACE=angiotensin-converting enzyme. NSAIDs=non-steroidal anti-inflammatory drugs.

Other factors, such as chemotherapy-induced nausea, vomiting, and diarrhoea, can lead to prerenal acute renal failure. The use of non-steroidal anti-inflammatory drugs (NSAIDs) can trigger acute kidney injury caused by reduced renal blood flow, tubular obstruction from crystal accumulation, direct cytotoxicity, and cell-mediated immune injury mechanisms. Other factors that might lead to acute kidney injury are sepsis, radiocontrast media, nephrotoxic co-medications (eg, bisphosphonates and NSAIDs), and some antibiotics, antimycotics, or antiviral drugs (eg, aminoglycosides, vancomycin, amphotericin B, or aciclovir). Finally, the presence of acute kidney injury can complicate allogeneic bone marrow transplantation because of volume depletion (vomiting or diarrhoea, or both), sepsis, graft-versus-host disease, and the use of nephrotoxic drugs such as calcineurin inhibitors (figure 1).[4,5]

Chronic kidney disease

As with acute kidney injury, chronic kidney disease appears to be both a potential cause and consequence of cancer. The increased risk of cancer in patients with chronic kidney disease is well established and patients with cancer have a greater occurrence of chronic kidney disease. Thus, it could be argued that kidney dysfunction creates an inflammatory microenvironment and oxidative stress, which can establish the ideal environment for cancer development.[6]

In support of this hypothesis, patients with end-stage renal disease have a higher risk of developing cancer than individuals with normal kidney function. The type of cancer is sex-dependent: liver, bladder, and kidney cancer are the three most common diseases in men with end-stage renal disease, whereas bladder, kidney, and breast

cancer occur at higher rates in women with this condition.[7] With the progressive ageing of patients on dialysis and their prolonged life expectancy, cancer is becoming much more prevalent in individuals with end-stage renal disease.[7] Patients on haemodialysis and peritoneal dialysis might also have different cancer risks, with a higher incidence of bladder and urinary tract cancer, hepatocellular carcinoma, and thyroid cancer in patients on peritoneal dialysis.[8]

In kidney transplant recipients, the incidence of cancer is even higher than for patients with chronic kidney disease.[9] In particular, Kaposi's sarcoma and skin cancer represent 75% of cancer cases in patients with transplants, although other types of solid tumours are also frequently encountered (eg, liver, kidney, and lung). Again, the increased rates of cancer in patients receiving a kidney transplant might be due, in part, to an inflammatory microenvironment and oxidative stress, as well as from infection with an oncogenic virus or treatment with immunosuppressive therapy.[9]

In a paper by Heaf and colleagues,[10] all patients with biopsy-diagnosed glomerulonephritis between 1985 and 2015 in Denmark were extracted from the Danish Renal Biopsy Registry and the National Pathology Data Bank. The authors found that cancer rates increased for many types of cancers. For reasons that have not been completely elucidated, the glomerulonephritis diagnosis with the highest risk of cancer was a membranoproliferative type. This condition is an immune-complex disease triggered by tumour antigen formation and is probably caused by the inability of the host to efficiently clear these antigens.[11] The increased incidence of cancer is mainly confined to a range of 1 year before to 1 year after kidney biopsy; however, renal carcinomas and unclassified cancers showed an increased incidence 5 years after renal diagnosis, which might be related to the carcinogenic potential of therapy.

Patients with cancer often have kidney problems, including chronic kidney disease or acute kidney injury. The effect of chronic kidney disease in patients with cancer is clinically relevant because it markedly reduces the survival rate.[12] There are multiple causes of kidney disease in patients with cancer, including acute kidney injury, electrolyte imbalances, and acid-base disturbances.[13] These causes can be explained, in part, by the use of chemotherapeutic drugs.[14] Other causes of chronic kidney disease in patients with cancer are paraneoplastic glomerulopathies, such as membranous nephropathy, IgA nephropathy, minimal change disease, membranoproliferative glomerulonephritis, and extracapillary glomerulonephritis. Chronic kidney disease in patients with cancer is frequently associated with malignant ureteral obstruction leading to obstructive nephropathy. Neoplastic ureteral infiltrations associated with large tumour masses cause kidney injuries and reduce the glomerular filtration rate (GFR). The most common tumours triggering malignant ureteral obstruction are cervical, bladder, and prostate cancers, and obstruction by retroperitoneal fibrosis caused by radiotherapy. The prevalence of chronic kidney disease is high in individuals with kidney cancer (29%) and bladder cancer (46%): in both cancer types, chronic kidney disease has been observed before surgical treatment.[15] In one study, urogenital cancers of the kidney and bladder, the prostate and testis in men, and the ovary and uterus in women, were the most prevalent cancers (180 [46%] of 391) in patients with chronic kidney disease.[16] Another frequent cause of chronic kidney disease in patients with cancer is nephrectomy, which is the primary surgical treatment for local kidney cancer. The hazard of postsurgical chronic kidney disease is related to the surgical technique. The risk is higher in patients with kidney cancer who are treated with radical nephrectomy than for patients treated with a partial nephrectomy, and such differences might be related to nephron-sparing. After partial nephrectomy, there is a lower risk of reaching an estimated GFR (eGFR) of less than 60 mL/min per 1·73 m² than with radical nephrectomy (38·4% *vs* 58·7%).[17] In addition, other aspects of surgery are essential, such as the ischaemia time of renal artery clamping, the location, and the tumour size. Finally, besides the surgical problems, importance has been given to the baseline features and comorbidities of patients.

Toxicity of chemotherapeutic drugs

Conventional cytotoxic agents

Systemic anticancer treatment can damage the kidney directly (eg, cisplatin-induced necrosis of the proximal tubule) or indirectly (eg, methotrexate-induced crystal nephropathy and tumour lysis syndrome). Nephrotoxicity is a serious adverse drug reaction of conventional cytotoxic chemotherapeutic agents and can affect the efficacy of cancer treatment and the survival of the patient.[18,19]

One of the most well studied nephrotoxic chemotherapeutic drugs is cisplatin. Cisplatin, which is used as part of chemotherapeutic regimens for a wide array of different cancers, can cause acute kidney injury in 20–30% of cases.[20] Cisplatin-induced nephrotoxicity is due to mitochondrial damage that is a consequence of increases in mitochondrial reactive oxygen species.[21] Cisplatin accumulates in the S3 segment of the proximal tubule and promotes glutathione depletion and high amounts of mitochondrial reactive oxygen species (figure 2). This accumulation could be related to the selective uptake of cisplatin via active basolateral-to-apical transporters, such as CTR1 and SLC22A2 (previously known as OCT2), which are both expressed on the basolateral membrane of the S3 segment. Another notable adverse effect of cisplatin is hearing loss. To prevent toxicity, sodium thiosulfate has been administered in children affected by hepatoblastoma 6 h after cisplatin chemotherapy,[22] with other strategies discussed by Viggiano and colleagues.[23] Similarly, in-vivo studies suggest that teneligliptin, a DPP-4 inhibitor, might

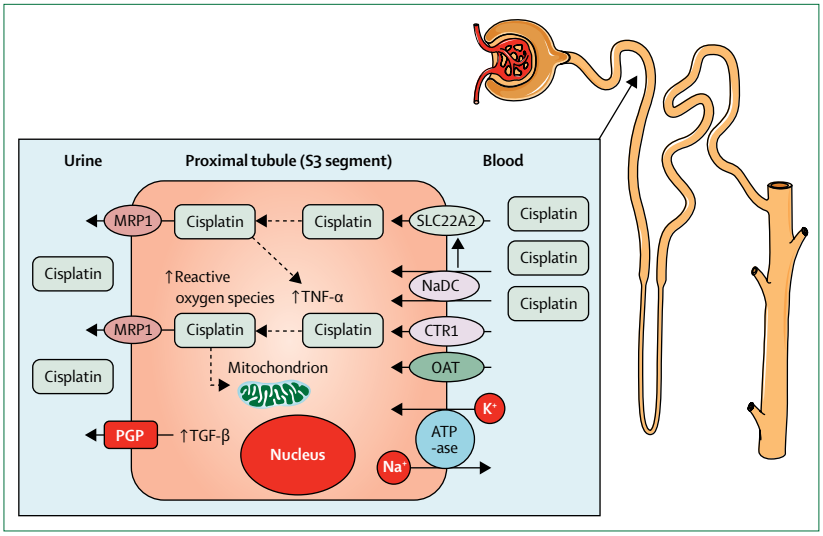

Figure 2: **Possible mechanisms of cisplatin renal toxicity in the proximal tubule**
Cisplatin is selectively taken up via an active basolateral-to-apical transporter, such as the CTR1 and SLC22A2 transporters, which are both expressed on the basolateral membrane of the S3 segment of the proximal tubule. Cisplatin accumulates in the cells and causes necrosis and apoptosis through different mechanisms (ie, reactive oxygen species, TNF-α signalling, and mitochondrial damage).

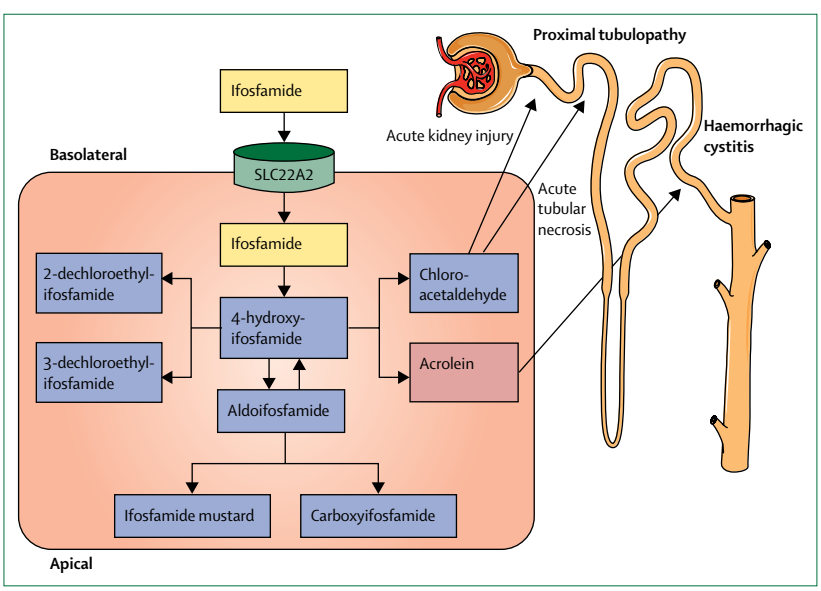

Figure 3: **Potential mechanisms of ifosfamide renal toxicity in the proximal tubule**
Ifosfamide is transported into proximal tubular cells via SLC22A2 on the basolateral membrane and is metabolised to chloracetaldehyde, which is toxic to the tubules and causes acute kidney injury, acute tubular necrosis, or proximal tubulopathy. Acrolein is another by-product causing haemorrhagic cystitis.

prevent cisplatin-induced nephrotoxicity and improve kidney function in patients with cancer by accelerating tubule regeneration and reducing injury and fibrosis.[24]

Other strategies to mitigate cisplatin-induced nephrotoxicity have been described.[25–28] For example, sirtuins, which are an evolutionarily conserved family of NAD+-dependent deacetylases with important antioxidant activity, appear to exert cytoprotective effects in the kidney, decreasing inflammation and apoptosis.[25] Importantly, in experimental cisplatin-induced acute kidney injury, a reduction in SIRT3 concentrations is coupled to oxidative stress and mitochondrial damage,[26] leading to metabolic and functional impairment of proximal tubular cells.[27] Subsequent studies have identified that honokiol, a natural biphenolic compound derived from the bark of magnolia trees, is a SIRT3 activating compound that has anti-inflammatory, antioxidative, antitumour, and nephroprotective actions. The use of honokiol also prevents the induction of cardiac fibrosis by attenuating fibroblast proliferation and transformation into myofibroblasts.[28] Ifosfamide is a synthetic structural isomer of a non-nephrotoxic cyclophosphamide and is used alone or concurrently with other drugs (eg, cisplatin, etoposide, and vinblastine) to treat metastatic germ-cell testicular cancer and some sarcomas.[29] Metabolites of ifosfamide, rather than the parent drug, are directly toxic to tubular cells (figure 3). Chloroacetaldehyde and isophosphoramide mustard might contribute to proximal tubulopathy with acute tubular necrosis and acute kidney injury, whereas another metabolite, acrolein, is believed to cause haemorrhagic cystitis.[29–31] The proposed mechanism of injury is cellular oxidative stress, leading to mitochondrial damage and energy depletion as well as disruption of cell membrane function.[30,31]

Another conventional cytotoxic chemotherapeutic drug that can cause nephrotoxicity is methotrexate. Methotrexate is used in patients with osteosarcoma (incidence of nephrotoxicity, 1·8%) and in haematological malignancies (incidence of nephrotoxicity not well characterised).[32] Glucarpidase, a bacterial enzyme, can reduce the toxicity induced by the administration of methotrexate. This enzyme can decrease serum methotrexate concentrations in patients with impaired renal function to less than 1 μM/L.[33]

Gemcitabine therapy (used in pancreatic, pulmonary, and breast cancers) has been associated with thrombotic microangiopathy, which is a rare pathology with a poor prognosis.[34] Eculizumab is a C5 inhibitor that has been successfully used in the treatment of gemcitabine-induced thrombotic microangiopathy.[35] Concerning anti-VEGF therapy, nephrotic-range proteinuria due to structural damage of the glomerular filtration barrier has been reported in 1–2% of patients treated with bevacizumab.[36]

There are many examples of anticancer drugs associated with nephrotoxicity, and preventive measures can be taken to manage these adverse effects (table 2).

The nephrotoxicity of chemotherapy (caused directly by the drug or its metabolites) is usually related to the dose and its repeated administration. Drugs that are primarily eliminated by the kidneys and are found at a high concentration in the renal tubule, or biotransformation of the drug in renal tubular cells with the production of reactive oxygen species, are associated with high renal toxicity. As already mentioned, co-medications might be a contributing factor (such as NSAIDs or aminoglycosides).[37]

	Clinical kidney syndrome	Histopathology of the kidney	Prevention	Treatment
Chemotherapeutics				
Gemcitabine, mitomycin C, or cisplatin (rare)	Acute kidney injury; hypertension (new or worsened); haematuria; proteinuria	Thrombotic microangiopathy	Gemcitabine should be used with caution in patients with renal insufficiency	Drug discontinuation and supportive care; if drug-induced thrombotic microangiopathy does not improve, the use of eculizumab (C5 inhibitor) should be considered
Platins (cisplatin, carboplatin, or oxalaplatin)	Acute kidney injury; thrombotic microangiopathy; Fanconi-like syndrome; nephrogenic diabetes insipidus; syndrome of inappropriate antidiuresis; Na^+ and Mg^{2+} wasting with hypomagnesaemia	Acute tubular injury and vasoconstriction in the renal microvasculature	Intravenous fluids with K^+ and Mg^{2+}; dose adjustment; substitution of cisplatin with a less toxic carboplatin; repeat courses of cisplatin should not be given until serum creatinine is <1·5 mg per day	Discontinuation of cisplatin; treatment of hypomagnesaemia with high-dose magnesium sulfate might be required since raising the plasma Mg^{2+} increases urinary Mg^{2+} wasting
Ifosfamide	Acute kidney injury; proximal tubulopathy (hypophosphataemia, Fanconi syndrome, renal tubular acidosis type 2); distal tubulopathy (renal tubular type 1, nephrogenic diabetes insipidus); syndrome of inappropriate antidiuresis	Acute tubular injury and acute interstitial nephritis (rare)	Intravenous fluids; dose adjustment; reducing the cumulative ifosfamide dose	NA
Pemetrexed	Acute kidney injury; proximal tubulopathy; Fanconi syndrome; renal tubular acidosis type 2; nephrogenic diabetes insipidus	Acute tubular injury, interstitial edoema, and interstitial fibrosis	Intravenous fluids; CT scans with contrast should be done a few days to 1 week after pemetrexed administration	NA
Methotrexate	Acute kidney injury; syndrome of inappropriate antidiuresis	Crystalline nephropathy and acute tubular injury	Dose reduction; intravenous fluids; urinary alkalinisation; high-dose leucovorin and glucarpidase; suspending medications that interfere with methotrexate clearance	Continuing to administer alkalinised intravenous fluids with the addition of acetazolamide to keep urine pH >7; use of extracorporeal techniques have mixed results; use of glucarpidase in patients with delayed methotrexate clearance due to impaired renal function (toxic methotrexate plasma concentrations >1 μM despite adequate preventive measures)
Anti-metabolites (azacitidine, capecitabine, clofarabine, fludarabine, 5-fluorouracil, mercaptopurine, or thioguanine)	Acute kidney injury; Fanconi syndrome; nephrogenic diabetes insipidus	Acute tubular injury	Intravenous fluids; dose reduction	NA
Vincristine or cyclophosphamide	Syndrome of inappropriate antidiuresis; haemorrhagic cystitis (cyclophosphamide)	No renal histopathological lesion	Intravenous fluids; use mesna to reduce haemorrhagic cystitis with cyclophosphamide	NA
Nitrosoureas	Chronic kidney disease	Chronic interstitial nephritis	Intravenous fluids	NA
Targeted cancer drugs				
Anti-VEGF drugs (bevacizumab or aflibercept)	Acute kidney injury; proteinuria (might be nephrotic); hypertension	Thrombotic microangiopathy	NA	Treatment of thrombotic microangiopathy with drug discontinuation and supportive care
Tyrosine kinase and multikinase inhibitors (sunitinib, sorafenib, pazopanib, or imatinib)	Acute kidney injury; proteinuria; hypertension	Thrombotic microangiopathy, focal segmental glomerulosclerosi, acute interstitial nephritis, and acute tubular injury (all these histopathologies have been seen with imatinib)	NA	Treatment of thrombotic microangiopathy with drug discontinuation and supportive care
EGFR inhibitors (cetuximab, panitumumab, gefitinib, or erlotinib)	Hypomagnesaemia; other electrolyte disorders	No renal histopathologic lesion	NA	NA
BRAF inhibitors (vemurafenib or dabrafenib)	Acute kidney injury; electrolyte disorders	Acute tubular injury, allergic acute, and interstitial nephritis	NA	NA
ALK inhibitors (crizotinib)	Acute kidney injury; electrolyte disorders; hypophosphataemia; proteinuria; haematuria; renal microcysts on ultrasound	Acute tubular injury and acute interstitial nephritis	NA	NA
Rituximab	Acute kidney injury (in tumour lysis syndrome); electrolyte distrubances	Crystalline (uric acid) nephropathy and acute tubular injury	Intravenous fluids	NA

(Table 2 continues on next page)

	Clinical kidney syndrome	Histopathology of the kidney	Prevention	Treatment
(Continued from previous page)				
Immunotherapy				
Interferons	Acute kidney injury; nephrotic proteinuria	Thrombotic microangiopathy and focal segmental glomerulosclerosis	NA	Treatment of thrombotic microangiopathy with drug discontinuation and supportive care
IL-2 (high dose)	Capillary leak syndrome with acute kidney injury (prerenal injury or acute tubular injury)	No kidney lesions (prerenal) or acute tubular injury	Intravenous fluids; reduce NSAID exposure	NA
CTLA-4 inhibitors (ipilimumab)	Acute kidney injury; proteinuria	Acute interstitial nephritis, lupus-like glomerulonephritis, acute tubular injury, minimal change disease, and thrombotic microangiopathy	Consider low-dose steroids with drug re-exposure	Acute interstitial nephritis might respond to treatment with corticosteroids; treatment of thrombotic microangiopathy with drug discontinuation and supportive care
PD-1 inhibitors (nivolumab or pembrolizumab)	Acute kidney injury; proteinuria; electrolyte disorders	Acute interstitial nephritis, acute tubular injury, minimal change disease, immune complex glomerulonephritis, and thrombotic microangiopathy	Consider low-dose steroids with drug re-exposure	Treatment of immune-related nephrotoxicity with drug discontinuation and supportive care; use of systemic steroids (depending on the severity of symptoms)
CAR T cells	Cytokine release syndrome complicated by capillary leak syndrome with acute kidney injury (prerenal injury or acute tubular injury); electrolyte disorders	No pathology oracute tubular injury	Reduce tumour burden with chemotherapy and steroid prophylaxis prior to CAR T-cell therapy; IL-6 receptor antagonism when cytokine release syndrome is severe	NA
Other cancer drugs				
Pamidronate	Nephrotic syndrome; acute kidney injury	Focal segmental glomerulosclerosis and acute tubular injury	Dose adjustment; increase infusion time	NA
Zoledronate	Acute kidney injury; nephrotic syndrome (rare)	Acute tubular injury	Dose adjustment; increase infusion time; contraindicated when GFR is <30 mL/min	NA
Androgen deprivation therapy	Acute kidney injury	Unknown	NA	NA
Arsenic trioxide	Acute kidney injury	Acute interstitial nephritis	NA	NA
Tamoxifen	Nephrotic syndrome	Minimal change disease	NA	NA

Na^+=sodium ion. Mg^{2+}=divalent magnesium ion. K^+=potassium ion. NA=not available. NSAID=non-steroidal anti-inflammatory drugs. CAR=chimeric antigen receptor. GFR=glomerular filtration rate.

Table 2: **Anticancer drug-related nephrotoxicity**

Patient-related factors associated with an increased risk of nephrotoxicity are age (>65 years), pre-existing chronic kidney disease, pharmacogenetics (eg, polymorphisms in the cytochrome P450 genes), or mutations in genes of cellular and renal transporters.[19]

Targeted agents

Targeted agents are the newest class of biological agents. Their discovery and development are a direct result of decades of basic and translational research into molecular targets that are aberrantly expressed in cancer cells. Examples of these molecular targets for which drugs have been developed include VEGF, VEGFR-associated tyrosine kinases, EGFR, HER2 (also known as ERBB2), BRAF, ALK, mTOR, and the 26S proteasome, among others. Despite the specificity of targeted agents for these signalling molecules, there are many off-target and adverse effects that directly or indirectly affect the kidney.

Targeting VEGF is essential for both normal and tumour-derived vasculogenesis and angiogenesis. Drugs targeting such molecules can cause kidney damage (usually reversible) characterised by podocyte damage or thrombotic microangiopathy, clinically associated arterial hypertension, proteinuria (non-nephrotic), or acute kidney injury.[38] This result is likely to be a direct effect of agents that target VEGF (eg, bevacizumab) because VEGF is produced by podocytes and crosses the glomerular basement membrane, binding to VEGF receptors on renal endothelium, mesangium, and peritubular capillaries.

Administration of anti-EGFR targeted monoclonal antibodies (eg, cetuximab, panitumumab, necitumumab, or matuzumab) is associated with hypomagnesaemia because of increased urinary magnesium loss. Magnesium reabsorption in the distal tubule is partly dependent on the activity of EGFR on transport proteins localised on the basolateral tubular membrane. Cetuximab prevents the binding of EGF to its tubular receptor with resultant hypomagnesaemia. By contrast, anti-HER2 agents, such as trastuzumab, pertuzumab, and lapatinib, which are mostly used for the treatment of breast cancer, might have indirect nephrotoxic actions on the kidney. Indeed, the cardiotoxicity shown with these drugs (enhanced by the

combination with anthracyclines) could result in cardiorenal syndrome.

BRAF is an important target in cancer that mediates cell growth and proliferation. Two prominent examples of inhibitors, vemurafenib and dabrafenib, block the kinase domain of a mutated version of BRAF and are used to treat patients with generalised *BRAF* Val600Glu-mutated melanoma. Vemurafenib can induce acute allergic interstitial nephritis (usually in the first 2 months of treatment and more frequently in men), acute tubular necrosis, and Fanconi syndrome due to proximal tubular cell damage with resulting electrolyte disturbances (eg, hypophosphataemia, hyponatraemia, and hypokalaemia). Crizotinib, an ALK inhibitor, can treat non-small-cell lung cancer and has been linked with hypophosphataemia, decreased GFR, proteinuria, and haematuria (usually during the first 2 weeks of treatment).[39,40] Ibrutinib, which is also a tyrosine kinase inhibitor (inhibits BTK), is used in the treatment of chronic lymphocytic leukaemia and mantle cell lymphoma and is also associated with acute kidney injury.[41]

Proteasome inhibitors can also cause kidney damage. For example, the treatment of multiple myeloma with the proteasome inhibitor, carfilzomib, can cause thrombotic microangiopathy and podocytopathy, which frequently clinically present as acute kidney injury.[42] Finally, rituximab, a B cell depleting anti-CD20 monoclonal antibody used to treat B-cell lymphomas, appears to cause electrolyte disturbances and acute kidney injury, especially in patients with high tumour burden.[18]

Immunomodulators and immunotherapy

Recombinant human IL-2 can cause capillary leak syndrome with hypovolaemia and subsequent prerenal acute renal failure. Recombinant IFN-α can induce proteinuria or even nephrotic syndrome.[43] Thrombotic microangiopathy is uncommon, but has been observed in patients with chronic myeloid leukaemia treated with high doses of IFN-α for up to 60 months.[44] Immunotherapeutic agents, such as IFN-α, are used to treat many malignancies, including AIDS-related Kaposi's sarcoma, metastatic melanoma, and follicular non-Hodgkin lymphoma. This therapy can cause glomerular damages, such as minimal change disease and focal segmental glomerulosclerosis. Discontinuing IFN-α therapy and starting corticosteroids or plasma exchange can help to reduce these toxicities.[44]

Inhibitors of immune checkpoint proteins (PD-1, PDL-1, and CTLA-4) have been a major breakthrough as they reactivate the immune response against cancer. Treatment with nivolumab (anti-PDL-1 monoclonal antibody) can sometimes result in hypophosphataemia, proteinuria, and hypertension, whereas treatment with pembrolizumab (anti-PD-1 monoclonal antibody) can cause acute interstitial nephritis leading to acute renal failure in about 2% of patients. Ipilimumab, which is an anti-CTLA-4 antibody, is used in patients with advanced melanoma and metastatic renal cell carcinoma. Renal damage is rare, but can be severe, and is characterised by nephrotic syndrome, acute tubular necrosis, acute interstitial nephritis, and acute kidney injury, of which some patients might respond to treatment with corticosteroids.[37] In a systematic review and meta-analysis of 125 clinical trials involving 20 128 patients, 13 284 (66%) of individuals developed at least one adverse event of any grade.[45] The most common adverse events were fatigue, pruritus, and diarrhoea. Although renal complications with immune checkpoint inhibitors are not very common compared with other immune-related adverse events, physicians must recognise and manage these renal manifestations. Acute kidney injury is a rare complication with an incidence of less than 2% when on ipilimumab or nivolumab therapy.[46] A combination of these drugs results in a higher incidence of acute kidney injury in up to 5% of patients.[46] A similar trend and incidence were reported with the sequential administration of ipilimumab and nivolumab.[46]

The combined or sequential administration of anti-CTLA-4 and anti-PD-1 therapy should be considered a higher risk regimen for acute kidney injury than monotherapy. Thus, other causes of acute kidney injury should be explored first, such as volume depletion because of concomitant colitis and diarrhoea, inadequate fluid intake, renal obstruction, nephrotoxicity from antibiotics, NSAIDs, or proton-pump inhibitors, as well as concomitantly administered cytotoxic chemotherapy. However, in a single-centre study by Oleas and colleagues,[47] of 826 patients with solid organ malignancy treated with an immune checkpoint inhibitors, 125 (15%) developed acute kidney injury. The main presentation was proteinuria of subnephrotic range and eosinophiluria with acute interstitial nephritis by biopsy. The exact mechanism by which immune checkpoint blockade triggers acute interstitial nephritis remains unknown. The kidneys appear to be one of the most affected organs in patients treated with immune checkpoint inhibitors.[47,48] Depending on the severity of the symptoms, the management of renal immune-related adverse events includes discontinuation of the agents with or without systemic steroid treatment.[49]

Radiotherapy

Radiotherapy is an essential and frequently used tool to treat patients with cancer. Approaches to improve the efficacy and reduce the toxicity of radioimmunotherapy for the management of cancer has been discussed by Deutsch and colleagues.[50] Radiotherapy might also mediate robust immunostimulatory effects that could act synergistically with immunotherapy in systemic tumour control.[50] However, the use of radiotherapy (sometimes in combination with chemotherapy) in the treatment of renal and urogenital cancer, various lymphomas, and sarcoma might also lead to impairment of renal function.[51] Indeed, the incidence of radiotherapy-associated kidney damage increases with more frequent use of total body

irradiation, as is done before allogeneic bone marrow transplantation. Mechanistically, radiotherapy-induced oxidative damage of DNA results in delayed proteinuria, hypertension, and the impaired ability to concentrate urine. Radiotherapy might also be associated with retroperitoneal fibrosis, characterised by inflammation and the deposition of fibrous tissue around the abdominal aorta and iliac arteries. Importantly, retroperitoneal fibrosis can lead to ureteral obstruction.[51] This syndrome has been described in published literature since 1992, with a patient who had received cobalt retroperitoneal radiation therapy 13 years previously for stage 1 testicular seminoma.[52] First-line treatment for this syndrome is corticosteroids, which might also cause glomerulonephritis.[53,54] Perazella and colleagues[54] recommend that all patients with radiation-induced nephropathy should be followed up by nephrologists and urologists.

Hormonal and antiresorption agents

Androgen deprivation therapy is used in patients with prostate cancer. This hormonal therapy is associated with an increased risk of acute kidney injury (especially in combination with luteinising hormone-releasing hormone agonists and oral antiandrogens). The mechanism by which androgen deprivation therapy leads to nephrotoxicity remains unclear, but might relate to the absence of testosterone-induced renal vasodilation and tubular damage caused by the concomitant reduction of oestrogen.[55]

Denosumab, a monoclonal antibody against TNFSF11 (also known as RANKL), is used to treat patients with skeletal metastases and is not itself nephrotoxic, but can cause hypocalcaemia. By contrast, bisphosphonates (eg, alendronates, ibandronate, pamidronate, risedronate, and zoledronic acid) also block osteoclastic bone resorption but are nephrotoxic because of the inhibition of protein prenylation, resulting in acute tubular necrosis (zoledronate), podocyte damage with collapsing focal segmental glomerulosclerosis (pamidronate), or thrombotic microangiopathy.[56]

Assessment of kidney function in patients with cancer

The eGFR is essential in patients with cancer because this measurment helps clinicians to determine the optimal dose of anticancer drugs and, in turn, prevent the onset of nephrotoxic or systemic adverse drug reactions.[57] Furthermore, this value is an important prognostic factor for cancer survival.[58] However, measuring GFR is complex, and several formulae have been proposed to estimate GFR on the basis of serum creatinine. Unfortunately, patients with cancer often have a large deviation in body composition compared with the healthy population, which is partly due to cachexia and an associated decrease in total muscle mass. Since blood creatinine is linked to muscle mass, the sarcopenia in patients with cancer leads to a decreased serum creatinine concentration and resulting overestimation of the GFR. This value represents a risk of severe toxicity during chemotherapy.[59]

In published reviews on the assessment of kidney function in oncology, different methods of GFR measurement and the limitations of various formulae were discussed.[60,61] A new model by Janowitz and colleagues[62] was shown to improve the estimation accuracy for GFR compared with seven measurement models adjusted to body surface area. The new equation is even more accurate than body surface area-adjusted chronic kidney disease epidemiology and the Cockcroft-Gault formula.[62] Finally, a formula derived from creatinine plus cystatin C measurements could be the most accurate method to estimate GFR, both in the general population and in patients with chronic kidney disease.[63] Although data for the validation of this formula in patients with cancer are incomplete, cystatin C release might be affected by inflammation and cell turnover rate, which are two well described biological conditions in cancer.[64] In addition, Krens and colleagues[65] discussed the effect of renal and hepatic function on the pharmaco-kinetics of anticancer drugs. The authors also provide a practical set of recommendations for dose adjustments of 160 anticancer drugs for patients with impaired renal and hepatic function.

CAR T-cell therapy

CAR T-cell therapy represents a novel use of immunotherapy to treat various forms of cancers, such as leukaemia and lymphoma. The treatment consists of patients' immune cells that are genetically modified and subsequently reinfused.[66] A promising use of this novel therapy is in pancreatic cancer, which is an aggressive malignancy with few treatment options.[67] This therapy is associated with cytokine release syndrome and neurotoxicity. Neurotoxicity consists of delirium, cerebral oedema, and intracranial haemorrhage, which can complicate the prognosis of pancreatic cancer. CAR T-cell therapy targeting CD19 is associated with cytokine release syndrome and comprises of general inflammation, cardiomyopathy, and acute kidney injury (eg, tubular injury).[68] This syndrome is caused by the release of important cytokines like IL-1, IL-8, and IL-6. Acute kidney injury from CAR T-cell infusion is multifactorial and reversible. The most important cause of renal injury is reduced renal perfusion triggered by hypotension, which is a key characteristic of this set of symptoms. The cytokine-mediated vasodilation (IL-6, IL-1, IL-8) reduces renal perfusion and cardiac output.[69] In a study by Gupta and colleagues,[70] of 78 adults with diffuse large B-cell lymphoma receiving CAR-T therapy (axicabtagene ciloleucel or tisagenlecleucel) 66 (85%) had cytokine release syndrome, whereas acute kidney injury was diagnosed in 15 (19%). In addition, electrolyte abnormalities were observed, including 59 (75%) patients with hypophosphataemia, 44 (56%) with hypokalaemia, and 40 (51%) with hyponatraemia.[70] To prevent and treat these side-effects, CAR T-cell therapy could be combined with chemotherapy

to reduce tumour burden, with corticosteroids to lessen inflammatory response, with a vasopressor to treat hypotension (supportive care), and with tocilizumab (anti-IL-6 monoclonal antibody) to reduce the inflammatory response induced by IL-6 signalling. Tocilizumab has been approved by the US Food and Drug Administration (FDA) under the name of actemra (Roche Pharma AG, Grenzach-Wyhken, Germany).[71] An important challenge is the utilisation of CAR-T cell therapy to establish tolerance in transplantation or to re-establish tolerance in autoimmune kidney disease, including for antineutrophil cytoplasmic antibody-associated vasculitis, antiphospholipase A2 receptor membranous nephropathy, Goodpasture's disease, and even lupus nephritis and IgA nephropathy.[72]

Future research and unmet needs

Considerable advances have been made in the treatment and management of cancer. However, given the chronic nature of cancer treatment, better in-vitro and in-vivo preclinical models are needed to assess the biological activity, pharmacokinetics, and adverse drug reactions of novel treatments before deployment in clinical settings. Organotypic spheroid cultures generated from human and mouse tumours have been used to evaluate ex-vivo short-term responses to checkpoint blockade.[73,74] These systems do not have the capability to recapitulate the tumour microenvironment, T-cell priming, or the microbiome influence on tumour response.[75] To overcome such limitations, Neal and colleagues[76] have developed three-dimensional organoids that preserve the architecture of the tumour microenvironment, which includes functional tumour-infiltrating lymphocytes and a tumour stroma and parenchyma, allowing the opportunity for in-vitro models of intrinsic tumour microenvironment to evaluate responses to immunotherapies. Efforts have also been made in the in-vivo setting, with humanised mice proving to be a valuable animal model in the study of immuno-oncology based therapies.[77–79] Among the types of adoptive T-cell transfer therapies being developed for cancer treatment, autologous CAR T cells have been the first to gain US FDA approval. A principle challenge in treating solid tumours is the tumour microenvironment, which represents a major barrier for adoptive T-cell therapy and often leads to adaptive resistance.[74–80] These therapies are also associated with a high risk of developing severe cytokine release syndrome that can lead to nephrological and neurological toxicity, among others. Thus, more predictive preclinical models are needed to accurately evaluate safety and efficacy before testing in human clinical trials.

In the past few years, several clinical trials have shown that immunotherapies, such as CAR T cells and immune checkpoint inhibitors, improve survival for patients with a diverse subset of cancers, leading to the approval of these treatments by the FDA. Unfortunately, there are still a vast number of tumours that do not respond to such novel therapeutic approaches. A study in 2019 showed a correlation between the response of a tumour to immunotherapy and the tumour's mutational burden.[81] Therefore, novel strategies are needed to enhance tumour immunogenicity in these diseases. Moreover, there are efforts to identify novel therapies and combination treatments that can overcome such resistance. The ultimate goal is to increase the trafficking of T cells to tumours so that the chances of an immune response are increased.[82,83] In support of such novel strategies, better preclinical models are needed to screen for unacceptable toxicities, including nephrotoxicity. Thus, a combination of well designed preclinical studies, new preclinical models, and novel techniques for making tumours visible to the immune system hold the key to improving outcomes for patients with chemoresistant and unresponsive tumours.

In summary, given the complex and intertwined relationship between the kidney, cancer, and cancer chemotherapeutics, close collaboration between oncologists, nephrologists, intensivists, and palliative care specialists is essential. The advances in cancer management present new opportunities and challenges for the oncology and nephrology communities. Nephrologists should be informed and actively involved in certain facets of cancer care; a better understanding of cancer biology and cancer therapy is required for nephrologists to become valuable members of the cancer-care team and to provide the best nephrology care possible. The development of more effective cancer treatments has led to an increasing number of patients that survive cancer, but unfortunately many of these treatments can also be nephrotoxic. Therefore, the prevention, early detection, long-term monitoring, and treatment of ensuing renal problems in these patients is a growing need in this population. By contrast, in the setting of advanced malignancy complicated by multiorgan illness, the appropriateness of aggressive treatment and the role of palliative therapy remains an open question. The use of persistent therapy (eg, a continuation of kidney replacement therapy in advanced malignancy) versus end-of-life care is also a scenario that more clinicians are facing today. As new therapies and novel techniques are expanding there is a need for well designed preclinical and clinical studies, and the recognition of therapy drawbacks, in order to introduce timely appropriate management.

Contributors

JM and GC conceived the work and contributed to the design of the research. JM, PT, GC, and AC prepared the manuscript. All authors edited and approved the final version of the manuscript.

Declaration of interests

PT reports personal fees from Amgen, Eisai, Elli Lilly, Novartis, Pfizer, and Roche. A Cancer Prevention and Research Institute of Texas grant (160093) did not sponsor AC's salary during the submitted work. All other authors declare no competing interests.

Acknowledgments

Expert assistance from Michael Lee in the review of this paper is gratefully acknowledged.

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