KDIGO Controversies Conference on onco-nephrology: understanding kidney impairment and solid-organ malignancies, and managing kidney cancer

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The association between kidney disease and cancer is multifaceted and complex. Persons with chronic kidney disease (CKD) have an increased incidence of cancer, and both cancer and cancer treatments can cause impaired kidney function. Renal issues in the setting of malignancy can worsen patient outcomes and diminish the adequacy of anticancer treatments. In addition, the oncology treatment landscape is changing rapidly, and data on tolerability of novel therapies in patients with CKD are often lacking. Caring for oncology patients has become more specialized and interdisciplinary, currently requiring collaboration among specialists in nephrology, medical oncology, critical care, clinical pharmacology/pharmacy, and palliative care, in addition to surgeons and urologists. To identify key management issues in nephrology relevant to patients with malignancy, KDIGO (Kidney Disease: Improving Global Outcomes) assembled a global panel of multidisciplinary clinical and scientific expertise for a controversies conference on onco-nephrology in December 2018. This report covers issues related to kidney impairment and solid organ malignancies as well as management and treatment of kidney cancer. Knowledge gaps, areas of controversy, and research priorities are described.

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Kidney disease and cancer have a multifaceted association. Persons with chronic kidney disease (CKD) have an increased incidence of cancer relative to patients without CKD.[1,2] In addition, both cancer and cancer treatments can cause impaired kidney function, including acute kidney injury (AKI) or CKD. Renal issues in the setting of malignancy can worsen patient outcomes and diminish the adequacy of anticancer treatments. Patients whose cancer is potentially curable can experience multiorgan failure requiring intensive care and kidney replacement therapy. In some countries, the amelioration of cancer mortality caused by greater treatment efficacy has resulted in a growing population of cancer survivors[3] who are at increased risk for kidney disease. Finally, advanced malignancy complicated by multiorgan illness raises questions related to the appropriateness of aggressive treatment versus palliative therapy.

The complex relationship between kidney disease and cancer is confounded by a rapidly changing treatment landscape. Caring for oncology patients has become more

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specialized and interdisciplinary, currently requiring collaboration among specialists in nephrology, medical oncology, critical care, clinical pharmacology/pharmacy, and palliative care, in addition to surgeons and urologists. To identify key management issues in nephrology relevant to patients with malignancy, KDIGO (Kidney Disease: Improving Global Outcomes) assembled a global panel of multidisciplinary clinical and scientific expertise for a controversies conference on onco-nephrology in Milan, Italy in December 2018. This report covers issues related to kidney impairment and solid organ malignancies as well as management and treatment of kidney cancer. Knowledge gaps, areas of controversy, and priorities for research are described.

KIDNEY IMPAIRMENT AND SOLID ORGAN MALIGNANCIES

CKD is highly prevalent in cancer patients; the prevalence of estimated glomerular filtrate rate (eGFR) <60 ml/min per 1.73 m^2 in cancer patients is estimated to be 12% to 25%.[4–9] Certain cancers, such as renal cell carcinoma (RCC)[7,10] and bladder cancer,[11] have a higher prevalence of CKD than others. The presence of CKD worsens the survival rates of cancer patients.[5,8,12–14] Patients with CKD G5 are at a higher risk of certain types of cancers: kidney, bladder, and infection-associated cancers such as tongue, liver, and cervix.[15–19] In men, CKD G3 or higher has been associated with an elevated risk of urinary tract cancers.[20] It is unknown why patients with CKD have an increased cancer-related mortality relative to those who do not have CKD (Table 1).[21,22]

Pathophysiologic causes and mechanisms of AKI and CKD in solid cancers have prerenal (e.g., volume depletion, hypotension, vascular compression, cancer cachexia), renal (e.g., glomerular diseases, tubulointerstitial disease, renovascular disease), and postrenal (e.g., bulky obstruction, urinary retention, nephrolithiasis) origins.[23,24] Common cancer therapies that can induce AKI are listed in Table 2.[21,24]

Assessment of kidney function

Precise GFR measurement is crucial when deciding treatment and drug dosing, and monitoring kidney function. Unfortunately, all available formulas can under- or overestimate GFR.[25] In addition, the presence of sarcopenia causes inaccuracies in GFR estimation. Different creatinine-based equations are used to estimate GFR in cancer: the Cockcroft-Gault formula, the Modification of Diet in Renal Disease study equation, and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. However, these models for GFR estimation were developed mainly in non-cancer populations, and their usefulness in the oncologic settings is uncertain. Recently a large study by Janowitz *et al.* 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, based on comparison with radioisotopic clearance with chromium-51 ethylenediamine tetraacetic acid.[26] The online GFR calculator is available at http://tavarelab.cruk.cam.ac.uk/JanowitzWilliamsGFR/.

The conference workgroup agreed the CKD-EPI equation[27] is the current best approach for dosing chemotherapeutic agents in patients with CKD. The use of cystatin C–based equations can confer better accuracy in predicting elimination of drugs by the kidneys[28]; however, with targeted oncology treatments, cathepsin D–mediated proteolysis may lower cystatin C irrespective of kidney function. Therefore, universal use of cystatin C-based equations is not recommended.[29] Use of the Cockcroft-Gault formula in determining dosing of chemotherapeutic agents is problematic because it may underestimate creatinine clearance, leading to inappropriate dose reductions of cancer treatments.[30] Better methods for estimating GFR are needed, as are point-of-care tests that can rapidly measure GFR.[31,32]

Applicability and efficacy of various diagnostics in the onco-nephrology setting

Renal investigations in patients with solid-organ malignancies. For patients with solid organ malignancy, the key renal investigations at diagnosis are assessment of kidney function, comorbidities, acid-base balance, and electrolytes, as well as urine analysis. Renal ultrasound is useful in cancer patients who develop AKI, unless the kidneys have already been adequately evaluated with other radiologic imaging. In candidates for nephrectomy, renal scintigraphy can be used to evaluate single-kidney function, or it can support choice of radical versus partial surgery with RCC. During oncologic treatment, for patients with or without AKI, renal investigations would include the usual follow-up tests based upon type of cancer and therapies. For patients in whom AKI is developing (Supplementary Table S1),[33] key renal assessments are similar to those suggested at cancer diagnosis, with the addition of spot urine protein-to-creatinine ratio. During follow-up after cancer treatment, nephrology consultations are indicated if patients show changes in kidney function or increasing proteinuria.

Cancer screening in dialysis patients. Cancer screening in the setting of kidney failure can be cost-effective if the expected survival is long enough or the patient is a transplant candidate. Conversely, comprehensive screening in patients with a limited life expectancy may not be beneficial.[34] Therefore, decisions regarding cancer screening in patients with CKD G5 should be made on an individual basis, taking into account expected survival, risk factors, and transplant status.

Cancer screening in patients with glomerulonephritis. All patients with membranous nephropathy, particularly those older than 60 years, should be considered for cancer screening following age-appropriate guidelines. Patients with membranous nephropathy who have features of secondary membranous nephropathy on kidney biopsy (subendothelial or mesangial deposits, >8 white blood cells per glomerulus, non-IgG-4 subtype) should be more intensively screened for underlying malignancy.[35] Patients with minimal change disease who have unexplained anemia, abnormal serum protein electrophoresis, hepatosplenomegaly, or lymphadenopathy

Table 1 | Research priorities in understanding kidney impairment and solid organ malignancies, and managing kidney cancer

	Research priorities
Kidney impairment	• Identify the reasons why CKD patients have an increased cancer-related mortality vs. non-CKD patients • Develop better methods for estimating GFR • Develop point-of-care tests that can rapidly measure GFR • Identify panels of novel biomarkers for determining GFR[21] • Create a biobank of kidney samples (additional core samples) or an international biopsy registry (with direct data input and shared databases from national registries) for cancer patients with kidney complications
Cancer screening	• Evaluate the cost-effectiveness of cancer screening in CKD G5 patients • Evaluate whether renal cystic disease is associated with cancer • Identify optimal tools for cancer screening and timing in CKD G5 patients with renal cystic disease • Evaluate the cost-effectiveness of cancer screening in patients with glomerulonephritis • Determine whether patients who are negative for anti-phospholipase A_2 receptor or positive for thrombospondin type-1 domain-containing 7A are at increased risk of developing cancer-related membranous nephropathy
Preventing CKD or AKI	• Analyze CKD-specific outcomes data for ACE inhibitors or ARBs in VEGF-associated hypertension/proteinuria • Analyze CKD-specific outcomes data for RAS inhibition in malignancies such as urinary tract malignancies, gastric cancer, and hepatocellular carcinoma • Perform a controlled study evaluating whether reducing contrast dose and using iso-osmolar contrast media in patients with CKD G4–G5 are preferable to not performing CT scans • Perform a randomized controlled trial of iso-osmolar vs. low-osmolar contrast media in cancer patients with CKD G3b–G4, stratified for outpatients and inpatients • Evaluate oral vs. i.v. hydration in cancer patients with CKD G3b–G5 (not treated by dialysis) undergoing repeated CT scans

Nephrotoxicity	• Identify predictors of nephrotoxicity
	• Evaluate the effects of long-term steroid treatment used to prevent recurrence of immune-mediated nephrotoxicity
	  ○ Biopsy studies are important, because not all renal complications are steroid-sensitive interstitial nephritides
	• Create registry studies to better understand cancer-related survival in cancer patients treated with ESAs
	• Evaluate new anemia treatments that stimulate endogenous erythropoietin production and enhance iron availability, such as hypoxia-inducible factor prolyl hydroxylase inhibitors,[22] in cancer patients with CKD
	  ○ Prospectively evaluate risk of inducing cancer-stimulating angiogenesis
	• Determine pharmacokinetics and pharmacodynamics of anticancer drugs in peritoneal dialysis and in CKD G5 patients

Managing kidney cancer	• Evaluate use of checkpoint inhibitors prior to cytoreductive surgery • Evaluate use of checkpoint inhibitors in patients with kidney disease, including those undergoing dialysis

ACE, angiotensin-converting enzyme; AKI, acute kidney injury; ARB, angiotensin II receptor blocker; CKD, chronic kidney disease; CT, computerized tomography; ESA, erythropoiesis-stimulating agent; GFR, glomerular filtration rate; RAS, renin-angiotensin system; VEGF, vascular endothelial growth factor.

should also be screened for underlying malignancy, especially Hodgkin lymphoma.[36]

Kidney biopsy in cancer patients with urinary abnormalities. Kidney biopsy should be considered in cancer patients with significant new-onset proteinuria (defined as >1 g/d by conference participants) or worsening kidney function, when the diagnosis of kidney disease cannot be otherwise established and may change care management. Kidney biopsy should not be performed in cancer patients with a poor prognosis; if the expected gain for an appropriate diagnosis is less than the patient's expected survival, then biopsy is unlikely to be useful.

In patients with kidney cancer undergoing surgery, non-neoplastic kidney tissue examination is highly recommended to identify coexisting kidney parenchymal diseases.[37,38] The indication for kidney biopsy in cancer survivors, without active cancer and a good prognosis, should be similar to general population guidelines. However, biopsy and eventually rebiopsy could be considered for evaluating long-term consequences of systematic therapy and radiation-induced kidney toxicity.[38,39]

To date, too few biopsies are being performed in cancer patients with kidney complications. Indeed, a biobank of kidney samples or an international biopsy registry could be helpful in understanding the spectrum of disease and outcomes (Table 1).

Preventing development or progression of AKI or CKD

Angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers in CKD or nephrectomized cancer patients. Angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) should be considered in nephrectomized patients with CKD in whom there is clinical indication for renin-angiotensin system (RAS) inhibition (e.g., hypertension, proteinuria, or cardiac indication).[40–42] ACE inhibitors or ARBs may be beneficial in patients with vascular endothelial growth factor (VEGF) inhibitor−associated hypertension/proteinuria, although CKD-specific outcomes data are needed. ACE inhibitor or ARB use in patients with cancer may be associated with improved overall survival.[43–48] A meta-analysis including 11 studies showed benefits in urinary tract cancer (hazard ratio [HR] 0.22), colorectal cancer (HR 0.22), pancreatic cancer (HR 0.58), and prostate cancer (HR 0.14), but not in breast cancer or hepatocellular carcinoma.[47] The meta-analysis indicated that using ACE inhibitors or ARBs in cancer

Table 2 | Common anticancer drugs associated with acute kidney injury

Medication	Mechanism of action	Renal histopathologic features	Clinical nephrotoxic effects
Chemotherapeutic agents			
Cisplatin[a]	Cross-linking and interference with DNA replication	Acute tubular injury and acute tubular necrosis	Acute kidney injury, proximal tubulopathy, Fanconi syndrome, NDI, sodium and magnesium wasting
Ifosfamide	Nitrogen mustard alkylating agent; inhibition of DNA synthesis through DNA strand-breaking effects	Acute tubular injury and acute tubular necrosis	Acute kidney injury, proximal tubulopathy, Fanconi syndrome, NDI
Pemetrexed	Antifolate agent; inhibition of dihydrofolate reductase, thymidylate synthase, and glycinamide ribonucleotide formyltransferase	Acute tubular injury and acute tubular necrosis	Acute kidney injury, proximal tubulopathy, Fanconi syndrome, NDI
Methotrexate	Antifolate agent; inhibition of dihydrofolate reductase	Crystalline nephropathy and acute tubular injury	Acute kidney injury
Pamidronate	Pyrophosphate analogue; associated with moderate FPPS inhibition	Focal segmental glomerulosclerosis, acute tubular injury	Nephrotic syndrome, acute kidney injury
Zoledronic acid	Pyrophosphate analogue; associated with potent FPPS inhibition	Acute tubular injury and acute tubular necrosis	Acute kidney injury
Targeted agents			
Anti-VEGF drugs	VEGF-receptor antibody or soluble receptor; inhibition of VEGF signaling	Thrombotic microangiopathy	Acute kidney injury, proteinuria, hypertension
Tyrosine kinase or multikinase inhibitors (sunitinib, sorafenib, pazopanib)	Inhibition of tyrosine kinase or multikinase signaling, with activity against RAF kinase and several receptor tyrosine kinases (e.g., VEGF, PDGF)	Thrombotic microangiopathy, focal segmental glomerulosclerosis, tubulointerstitial nephritis	Acute kidney injury, proteinuria, hypertension
BRAF inhibitors (vemurafenib and dabrafenib)	Inhibition of the mutated BRAF V600E kinase that leads to reduced signaling through the aberrant MAPK pathway	Acute tubular injury, tubulointerstitial nephritis	Acute kidney injury, electrolyte disorders
ALK inhibitors (crizotinib)	Inhibition of the mutated anaplastic lymphoma kinase	Acute tubular injury, tubulointerstitial nephritis	Acute kidney injury, electrolyte disorders, renal microcysts
Immunotherapeutic agents			
Interferons	Activation of STATs, which are transcription factors that regulate immune system gene expression	Thrombotic microangiopathy, glomerulopathies (e.g, focal glomerulosclerosis, membranous nephropathy, lupus-like nephritis, minimal change disease)	Acute kidney injury, nephrotic proteinuria
CTLA-4 inhibitors	T-cell activation by antibody blocking CTLA-4 receptor	Tubulointerstitial nephritis, lupus-like glomerulonephritis[b]	Acute kidney injury, proteinuria
PD-1 inhibitors	T-cell activation by antibody blocking PD-1 receptor	Tubulointerstitial nephritis[b]	Acute kidney injury
Chimeric antigen receptor T cells	T-cell targeting of specific tumor-cell antigens	No pathologic features described	Capillary leak syndrome with prerenal acute kidney injury

ALK, anaplastic lymphoma kinase; BRAF, B-Raf kinase; CTLA-4, cytotoxic T-lymphocyte antigen 4; FPPS, farnesyl pyrophosphate synthase; MAPK, mitogen-activated protein kinase; NDI, nephrogenic diabetes insipidus; PD-1, programmed death 1; PDGF, platelet-derived growth factor; STAT, signal transducer and activator of transcription; VEGF, vascular endothelial growth factor.

[a]Carboplatin and oxaliplatin are less nephrotoxic than cisplatin.

[b]In some cases, tubulointerstitial nephritis is accompanied by granulomatous interstitial nephritis.

patients could lead to a 40% reduction in the risk of cancer recurrence and a 25% reduction in mortality risk. A separate meta-analysis including 55 studies indicated RAS inhibitors can improve the survival of cancer patients, depending on cancer type and type of RAS inhibitor.[48] The beneficial effect of RAS inhibition was shown in urinary tract malignancies, such as RCC, upper tract urothelial cancer, and bladder cancer, as well as gastric cancer and hepatocellular carcinoma. Again, CKD-specific outcomes data are needed.

ACE inhibitors or ARBs may be associated with increased AKI risk in patients receiving active systemic therapy,[49,50] and, therefore, treatment decisions should be made using an individualized approach in such patients. For example, temporary discontinuation of ACE inhibitors and ARBs may be considered during cancer treatment.

Contrast-induced AKI. Intravenous contrast-induced AKI is a relevant issue in cancer patients, especially in those with comorbidities and/or reduced GFR (CKD G3b–G5). High doses of contrast media and repeated contrast-enhanced scans may increase the risk of AKI. Stable ambulatory patients (outpatients) have a lower AKI risk compared with sick, unstable inpatients with similar GFR.[51] In non-cancer patients, those with CKD G4–G5 have a significantly higher incidence of contrast-induced AKI (13.6% vs. 2.7% in patients with CKD G3a–G3b), even after prophylactic i.v. hydration.[52] There have been no randomized studies of the risk of radiocontrast administration in oncology patients, and there are insufficient data to determine whether CKD patients with cancer should receive fewer contrast media computed tomography (CT) scans. In a retrospective analysis of cancer patients,[53] contrast-induced nephropathy (CIN) prevalence was 9% with pre-existing kidney disease (50% had irreversible CIN) and approximately 5% without kidney disease. Cicin *et al.*[54] reported a 4.5-fold higher risk of CIN among oncology patients undergoing CT within 45 days after completing chemotherapy relative to those not given chemotherapy or undergoing CT more than 45 days after completing chemotherapy. However, the concept of CIN has been questioned based on results of multiple propensity score-matched analyses encompassing more than 60,000 patients, including those with cancer, in whom AKI risk was not significantly different with contrast-enhanced versus unenhanced CT scans.[55,56] A systemic review demonstrated similar risks of AKI, dialysis initiation, and mortality with enhanced or unenhanced CT.[57]

An exaggerated fear of radiocontrast nephropathy could lead to withholding of beneficial diagnostic studies or interventions in CKD patients and reduce the diagnostic power of follow-up protocols. Therefore, CKD patients should not be denied a contrast media CT scan if benefits are believed to outweigh the risks of post-contrast AKI. In CKD G4–G5, reducing contrast dose and using iso-osmolar contrast media are preferable to withholding CT scans, although their cost-effectiveness should be validated by a controlled study.

Currently, periprocedural use of i.v. saline and/or oral hydration, depending on the GFR level, is often used, although the results of prospective studies and meta-analyses are somewhat conflicting.[58] For example, in the AMACING randomized controlled trial of non-cancer patients with CKD G3a–G3b, no prophylaxis was noninferior and cost-saving compared with i.v. hydration in preventing post-contrast AKI.[59] Results from the PRESERVE trial of more than 5000 non-cancer patients did not support efficacy of sodium bicarbonate and acetylcysteine in preventing post-contrast AKI.[60]

A randomized, controlled trial of iso-osmolar versus low-osmolar contrast media in cancer patients with CKD G3b–G4, stratified for outpatients and inpatients, is a priority for research (Table 1). A second priority would be evaluating oral versus i.v. hydration in cancer patients with CKD G3b–G5 (not treated by dialysis) undergoing repeated CT scans.

Managing renal toxicities from treatments

Nephrotoxicity of oncologic treatments. Radiation nephropathy can occur after hematopoietic stem cell transplantation or after treatment with radioisotopes. Anti-cancer drugs are a relatively common cause of acute and CKD as well as electrolyte and acid-base disturbances (Figure 1[24]). Anti-cancer drugs can be generally classified as (i) cytotoxic chemotherapeutic drugs, (ii) targeted cancer agents, and (iii) cancer immunotherapies (Table 2). Cytotoxic chemotherapeutic drugs are the most common cause of kidney injury and include a number of agents, such as the platinum-containing compounds (especially cisplatin), ifosfamide, gemcitabine, methotrexate, and pemetrexed. Acute tubular injury (ATI) is the most common kidney lesion; however, a number of other kidney lesions have also been described, such as thrombotic microangiopathy (TMA), podocytopathies, tubulopathies (Fanconi syndrome, salt and magnesium wasting, nephrogenic diabetes insipidus), acute/chronic tubulointerstitial nephritis, and crystalline nephropathy.

Targeted cancer drugs have become increasingly important for the treatment of various malignancies, but adverse renal effects also complicate therapy. Anti-angiogenesis drugs are associated with new or worsened hypertension, proteinuria (sometimes nephrotic), and lesions such as TMA, minimal change disease/focal segmental glomerulosclerosis, and acute interstitial nephritis (AIN). Other agents such as the B-Raf and anaplastic lymphoma kinase inhibitors cause AKI (ATI and AIN) less commonly, whereas proteasome inhibitors may be associated with TMA; notably, ALK anaplastic lymphoma kinase inhibitors (e.g., crizotinib) and CDK4 and CDK6 inhibitors (e.g., abemaciclib) may cause a noninjurious increase in serum creatinine owing to an inhibitory effect of these drugs on the secretion of creatinine, and this should be differentiated from genuine renal toxicity.[61,62] Epidermal growth factor inhibitors, in particular cetuximab, have been associated with hypomagnesemia from renal magnesium wasting.

Cancer immunotherapies may also cause kidney disease. The older immunotherapies and their effects are well known; interferon is associated with different types of glomerulonephritis (e.g., focal glomerulosclerosis, membranous nephropathy, lupus-like nephritis, minimal change disease), as well as with TMA, whereas high-dose interleukin 2 is associated with cytokine storm syndrome and capillary leak syndrome with prerenal AKI and ATI. Immune checkpoint inhibitors are a relatively new and effective therapy for an increasing number of solid cancers. These drugs have been described as causing AKI and proteinuria (sometimes nephrotic); AKI is due primarily to AIN, but ATI also occurs. Minimal change disease and immune complex–related glomerular disease have also been described with these drugs.

Both the mechanisms of nephrotoxicity of oncologic treatments and the best management strategies for such toxicity are largely unknown. Research approaches are described in Table 1. Nephrotoxicity should be included in the surveillance of patients treated with immunotherapy and reported in drug registries.

Erythropoietin-stimulating agents and iron therapy. Currently the indications for treatment with erythropoietin-stimulating agents (ESAs) and iron therapy are no different for CKD patients with or without malignancy.[63,64] Most available guidelines of nephrology and oncology suggest the same target hemoglobin level (10–12 g/dl).[63–66] KDIGO guidelines recommend a lower range of 9.0–11.5 g/dl.[67] Using a

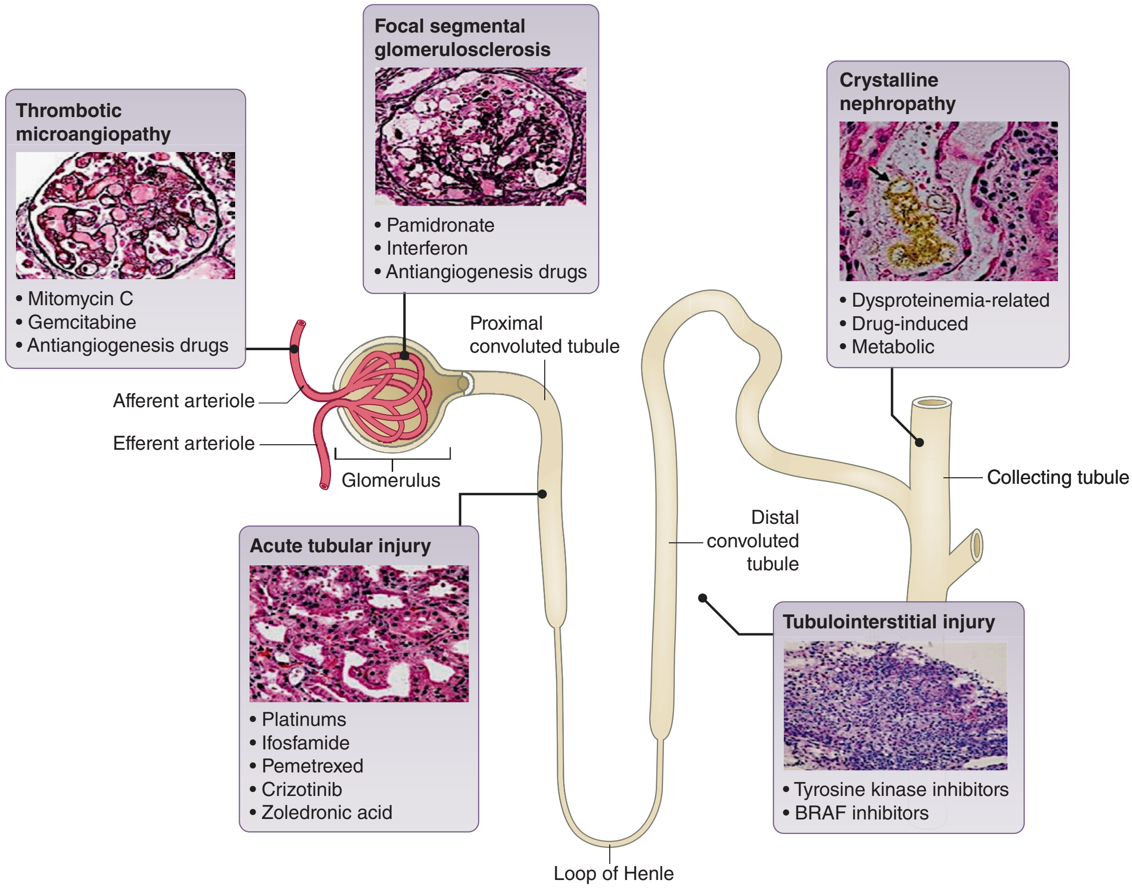

Figure 1 | Anticancer therapies and their site of action in the nephron. Drugs used to treat cancer can cause various forms of injury in sites in the nephron, such as the arterioles, glomerulus, tubules, and interstitium. In the image showing crystalline nephropathy, the arrow points to methotrexate crystals. The stains are Jones methenamine silver (thrombotic microangiopathy and focal segmental glomerulosclerosis images), hematoxylin and eosin (crystalline nephropathy and acute tubular injury images), and periodic acid–Schiff (tubulointerstitial injury image). BRAF (B-Raf kinase) denotes serine–threonine protein kinase. From *The New England Journal of Medicine*, Rosner MH, Perazella MA, Acute kidney injury in patients with cancer, volume 376, pages 1770–1781,[24] Copyright © 2017 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society. To optimize viewing of this image, please see the online version of this article at www.kidney-international.org.

range of 9–11.5 g/dl allows individualization for determining the best risk-benefit profile. For ESA, the nephrologic dose is suggested for cancer patients with CKD.[68] Meta-analysis data from 2009 have suggested treatment with ESAs in patients with cancer increases mortality and worsens overall survival[69]; however, a 2012 meta-analysis of 91 trials with more than 20,000 participants failed to show a direct impact of ESAs on cancer disease progression.[70] In a recent article, Thavarajah and Choi[71] underscored that while current evidence suggests ESAs may promote progression or worsen outcomes in some cancers, there are no data on the likelihood of developing new cancers in patients undergoing dialysis or those in earlier stages of CKD during ESA therapy.

Registry studies could aid in the better understanding cancer-related survival in cancer patients treated with ESAs. Evaluating new anemia treatments that stimulate endogenous erythropoietin production and enhance iron availability, such as hypoxia-inducible factor prolyl hydroxylase inhibitors,[22] in cancer patients with CKD will also be important.

Timing and dosing adjustments of anticancer drugs in patients with CKD G3–G5D. Available evidence suggests that failing to adjust the doses of anticancer drugs in patients with CKD is deleterious. In a prospective study of 143 colorectal cancer patients who received standard doses of capecitabine and oxaliplatin, among the 50 patients with creatinine clearance <60 ml/min, cytopenia and diarrhea were significantly higher relative to patients with creatinine clearance ≥ 60 ml/min, and efficacy of the drugs was reduced.[72] Alternatively, in a prospective study of more than 600 breast cancer patients, adjusting the dosage of anticancer drugs in patients with creatinine clearance <60 ml/min when necessary resulted in comparable toxicity and effectiveness relative to standard dosing in patients with creatinine clearance ≥60 ml/min.[73] In hemodialysis patients, active catabolites of certain drugs have the potential to accumulate and lead to unexpected adverse events,[74–76] and dose adjustment is crucial to avoid accumulation and toxicity. Published clinical recommendations regarding optimal timing and dose adjustment of anticancer drugs (also in timing related to the start of the

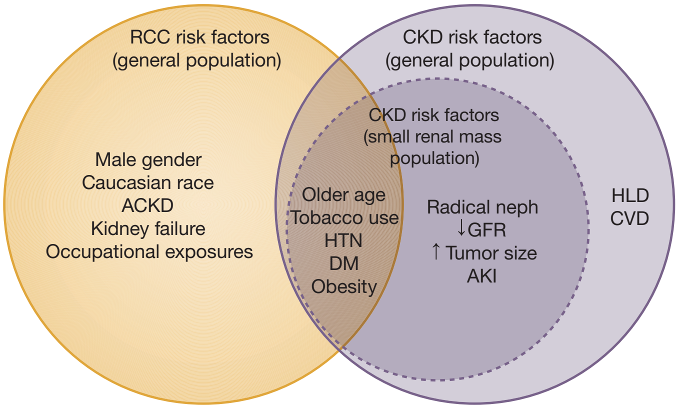

Figure 2 | Factors for both impaired kidney function and renal cell carcinoma. ACKD, acquired cystic kidney disease; AKI, acute kidney injury; CKD, chronic kidney disease; CVD, cardiovascular disease; DM, diabetes mellitus; GFR, glomerular filtration rate; HLD, hematopoietic and lymphoproliferative malignancies and related disorders; HTN, hypertension; neph, nephrectomy; RCC, renal cell carcinoma. Modified with permission from Hu SL, Chang A. Chapter 15: workup and management of "small" renal masses. Onco-Nephrology Curriculum. American Society of Nephrology. Available at: https://www.asn-online.org/education/distancelearning/curricula/onco/Chapter15.pdf. Accessed October 6, 2020.[88] Copyright © 2016 by the American Society of Nephrology.

dialysis session) in CKD G5D cancer patients do exist[77,78]; however, the recommendations were derived based on case reports or small case series. In additional, a nationwide study in Japan has indicated there is a gap between recommendations and clinical practice in dose adjustment of anticancer agents in CKD G5D patients.[79]

No data are available regarding advanced CKD and peritoneal dialysis patients, and therefore pharmacokinetic and pharmacodynamic studies are needed.

Decision-making for initiating or terminating kidney replacement therapy in patients with solid organ cancer. Currently, there is country-specific variation in approaches to starting or withholding dialysis in patients with solid organ (or hematologic) cancers. Although scoring systems to predict the survival of dialysis patients are available, they could and should be enhanced by including the presence of an active cancer and/or its prognosis. Withdrawal from chronic dialysis leads to death in a few weeks; therefore, when a cancer-related prognosis for survival is less than 2 weeks, dialysis should be stopped. Actively requesting advanced directives through interdisciplinary teamwork could help physicians and patients avoid making difficult decisions in emergency situations. Determining patients' preferences regarding long-term dialysis, time-limited trial dialysis, conservative CKD treatment, or palliative care is key.

MANAGEMENT AND TREATMENT OF KIDNEY CANCER

Epidemiology, prevalence, and type of renal cell carcinoma

The World Health Organization has estimated that the age-standardized incidence of kidney cancer worldwide was 4.5 per 100,000 persons in 2018.[80] RCC, which refers to cancer that originated from renal epithelium, accounts for >90% of cancers in the kidney.[81] RCC incidence predominates in men (1.5:1.0, males to females) and has a peak incidence in persons aged 60–70 years.[81] The incidence of RCC varies widely globally but is increasing in many countries.[82] The increased incidence is mainly related to changes in tumor detection and diagnostic practices (spread of CT/ultrasound), leading to the increase in diagnoses of early-stage RCC. Established risk factors are smoking, obesity, hypertension, CKD, diabetes, and certain genetic factors.[82] Whether physical activity, diet, alcohol consumption, and environmental exposures increase the risk for RCC is unclear.

Despite recent improvement in its treatment, RCC, when metastatic, remains a lethal disease. RCC mortality rates vary based on the extent of available urologic-oncology facilities and treatments.[83] In the majority of developed countries, RCC mortality rates are stable or decreasing as a result of screening efforts, early diagnosis, and improved treatments and their availability.[82]

Hereditary RCC syndromes account for 2% to 3% of all RCC cases,[84] and many gene variants have been associated with RCC.[84,85] The most common inherited cause of RCC is von Hippel-Lindau syndrome, in which there is a lifetime cumulative RCC incidence of approximately 70%.[84] Sporadic forms are generally associated with structural alterations of the short arm of chromosome 3.

Kidney function in RCC

Impaired kidney function is common in patients with RCC, either as a pre-existing condition or as a consequence of cancer and its therapy.[86] RCC and impaired kidney function share intrinsic kidney risk factors and systemic comorbidities (Figure 2).[87,88] Cancer-related risk factors for impaired kidney function in RCC include the following: malignant infiltration, which might involve renal parenchyma and/or renal vein and inferior vena cava; paraneoplastic syndromes caused by cytokine disease or immunogenic disease, including paraneoplastic nephropathies or hypercalcemia from parathyroid hormone–like protein production[89]; and obstruction of the urinary tract.

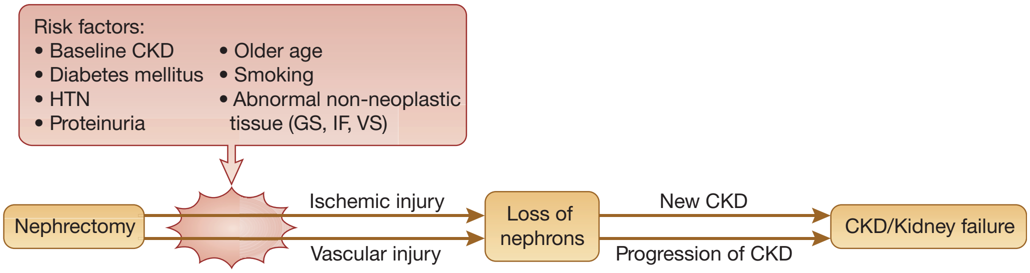

Figure 3 | Nephrectomy and chronic kidney disease (CKD). Vascular and ischemic injury resulting from nephrectomy can lead to nephron loss, which, in combination with risk factors and comorbidities, may result in *de novo* CKD or progression of existing CKD. AKI, acute kidney injury; GS, glomerulosclerosis; HTN, hypertension; IF, interstitial fibrosis; VS, vascular sclerosis. Modified from Hu SL, Chang A, Perazella MA, et al. The nephrologist's tumor: basic biology and management of renal cell carcinoma. *J Am Soc Nephrol.* 2016;27:2227–2237.[86] Copyright © 2016 by the American Society of Nephrology.

Surgical resection remains the preferred treatment modality in most cases of RCC. Unfortunately, nephrectomy has been recognized as an independent risk factor for kidney injury (Figure 3).[86,90] After nephrectomy, the reduction in renal mass is followed by a decrease in kidney function, especially in patients with pre-existing kidney disease; furthermore, the remaining glomeruli can incur hyperfiltration injuries.[87,91]

Patients with CKD are known to have an increased risk of RCC.[92,93] Although the cause of kidney cancer in CKD is unknown, several factors related to kidney injury have been proposed to explain this relationship,[94] including renal fibrosis and tubular atrophy, as well as uremia-related chronic inflammation, oxidative stress, compromised immune function, the dialysis process, medications, and comorbid diseases.[86] The risk of RCC is increased with increasing severity of kidney disease.[92] The observed association between CKD and future risk of RCC is not necessarily causative; individuals with impaired kidney function undergo more intensive medical surveillance relative to the general population, and this may lead to increased incidental detection of localized, indolent kidney tumors through abdominal imaging.

CKD is a prognostic factor for RCC and increases the risks of mortality,[95] cardiovascular events, kidney failure, and prolonged hospitalization.[10] Worsening kidney function can preclude or delay antineoplastic therapy. In addition, drug dosing may be inadequate in dialysis patients, who have increased clearance of certain drugs.

Type of surgery and kidney outcomes

Current guidelines recommend partial nephrectomy for the resection of tumors stage T1 (i.e., tumors ≤7 cm, confined to the kidney) to preserve as much normal renal parenchyma as possible.[96,97] The technique can also be considered for tumors staged T2 (i.e., tumors >7 cm, confined to the kidney) and T3a (i.e., tumors extending macroscopically into the renal vein, or affecting its branches, or invading the perinephric or renal sinus fat). Cytoreductive nephrectomy should not be performed in patients classified as poor risk based upon the Memorial Sloan Kettering Cancer Center classification.[98] Although criticized for methodology, the recently reported CARMENA and SURTIME randomized trials support offering systemic therapy prior to cytoreductive nephrectomy for metastatic RCC.[99,100] Reliable criteria for selecting patients for neoadjuvant tyrosine kinase inhibitors (TKIs) with cytoreductive nephrectomy remain largely elusive. Nevertheless, the results of the above-mentioned trials indicate that patients with risk features should be offered systemic therapy, and not cytoreductive nephrectomy, as the initial disease management. It is also important to stress that surgery is still a valuable tool in managing metastatic RCC. Therefore, intermediate-risk patients with potentially resectable metastases could be considered for cytoreductive nephrectomy and metastasectomy without systemic therapy as the initial disease management. Currently there are no data regarding use of checkpoint inhibitors prior to cytoreductive nephrectomy.

Concerns related perioperative risks and postoperative follow-up

Preventing CKD G5 after surgery involves identifying and reducing the risks of AKI and treating its complications.[91] Patients at risk for AKI include those with CKD, diabetes mellitus, hypertension, proteinuria, older age, or abnormal nonneoplastic tissue near the tumor, as well as patients who smoke.[91] Bhindi *et al.*[101] recently developed models for predicting kidney function outcomes after partial and radical nephrectomy based on these and other preoperative features; however, the formulas need to be validated and confirmed for generalizability. Having more accurate GFR measurements, better imaging, and better identification of risk groups would aid in processes related to prediction.

Intraoperative steps for preventing kidney injury include minimizing nephron loss and devascularization, avoiding irreversible ischemic damage, and maintaining adequate renal perfusion during surgery. A variety of pharmacologic manipulations (mannitol, dopamine, fenoldopam, antioxidants, growth factors, porphyrins, mitochondria-protecting amino acids) have been used in an effort to abrogate the negative effects of ischemia, although results of most translational studies to date have been negative. Intraoperative maneuvers for preventing irreversible ischemic injury include use of hypothermia, early unclamping, and zero ischemia. Results of a systematic review[102] indicate there is no evidence to suggest that limited ischemia time (≤25 min) has a higher risk of reduced kidney function after partial nephrectomy compared with a zero ischemia technique. Prolonged warm ischemia (>25–30 min) could cause an irreversible ischemic insult to the surgically treated kidney.

Postoperative general management includes having adequate follow-up with early recognition and timely intervention, early nephrologic referral of high-risk patients, avoiding postsurgery complications, avoiding nephrotoxins and renal hypoperfusion, and correcting reversible factors related to AKI. Strategies to prevent the progression of CKD to kidney failure include both regular monitoring of kidney function by measuring serum creatinine and eGFR, as well as prompt interventions to limit kidney disease onset or progression, including managing hypertension and diabetes mellitus, avoiding nephrotoxins and other aggravating factors, and correcting anemia, malnutrition, and metabolic acidosis. Repeated long-term monitoring of eGFR is indicated in cases of impaired kidney function before or after surgery.

New targeted therapies and renal side effects

Targeting agents for treating metastatic RCC include anti–vascular endothelial growth factor receptor/vascular endothelial growth factor treatments, mammalian target of rapamycin inhibitors, and immune checkpoint inhibitors. These are used as monotherapies and combination therapies. Anticancer drug−related nephrotoxicity is a common and notable cause of kidney injury, potentially causing hypertension, proteinuria, AKI, and electrolyte disorders.[91] Etiologies include acute tubular necrosis or injury and a variety of glomerular and vascular injuries.

Tyrosine kinase inhibitors. In patients undergoing dialysis, treatment with TKIs is safe and effective.[103–111] Retrospective studies indicate that the use of multitargeted TKIs (sorafenib, sunitinib, pazopanib, axitinib, cabozantinib, and lenvatinib) might prolong life expectancy in the setting of metastatic renal clear cell carcinoma, even in patients undergoing dialysis.[107]

Dialysis patients receiving TKIs do not require an increased number of dialysis sessions. Most adverse events with TKIs in dialysis patients are mild in severity, with anemia the most common adverse event reported.[103] Monitoring heparin use in dialysis patients undergoing TKI treatment may help to mitigate risk of bleeding. For patients not undergoing dialysis but with CKD G3a–G5, age and comorbidities are associated with increased blood pressure.[23] Blood pressure normalization at baseline and monitoring during treatment is of paramount importance,[112] although blood pressure control may be more challenging than in patients with better kidney function.[113] As a practical point, for patients with kidney disease, including those undergoing dialysis, TKIs may be started at a lower than standard dose and titrated up based upon tolerability. Because of the large distribution volume of TKIs, overhydration should be avoided with TKI use.

Immune checkpoint inhibitors. Although rare, autoimmune nephritis has been reported in patients treated with immune checkpoint inhibitors.[23] Serious renal toxicity (grade ≥3) is encountered in approximately 1% of patients and is usually reversed with discontinuation of the responsible agent and steroid therapy.[114] Checkpoint inhibitors can be restarted when prednisone dosing is ≤10 mg (although this recommendation is not supported by any prospective study). Nonsteroidal options include mycophenolate mofetil and rituximab and are indicated in the rare steroid-refractory cases. In selected cases of kidney injury, kidney biopsy can be considered.

Data on checkpoint inhibitors in patients with kidney disease or undergoing dialysis are extremely limited, generally to case reports or case series. Currently there is no evidence to support reducing the number of treatments with checkpoint inhibitors in patients with lowered GFR or undergoing dialysis.

CONCLUSIONS

Conference participants emphasized the importance of collaboration between nephrology and hematology/oncology specialists in clinical care as well as clinical trials.[115] Important gender-related issues in onco-nephrology that have not been investigated include epidemiology of cancer in CKD patients and of kidney impairment in cancer patients as well as response to cancer treatment in the setting of CKD. The limitations of current methods for estimating GFR and determining kidney function have negative clinical implications, and it is hoped that new approaches to measuring kidney function will be available in the near future. Nonetheless, hematology/oncology patients should undergo kidney function evaluations, including estimating GFR and determining the degree of proteinuria. In the setting of solid organ malignancy, important renal investigations include assessment of kidney function as well as comorbidities, acid-base balance, electrolytes, and urine analysis. In CKD patients, the current best approach for dosing chemotherapeutic agents is using the CKD-EPI equation. Postmarketing studies that include patients with CKD could inform dosing of oncology drugs in patients with CKD G3b–G5D, an area greatly lacking data. Trials specifically focused on RCC patients with impaired kidney function are an area of urgent need.

APPENDIX

Other conference participants

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Perazella, USA; Pierre Ronco, France; Mitchell H. Rosner, USA; Maria Jose Soler Romeo, Spain; Ben Sprangers, Belgium; Walter M. Stadler, USA; Paul E. Stevens, United Kingdom; Vladimír Tesař, Czech Republic; Verônica Torres da Costa e Silva, Brazil; David H. Vesole, USA; Anitha Vijayan, USA; Ondřej Viklický, Czech Republic; Biruh T. Workeneh, USA; Motoko Yanagita, Japan; Elena Zakharova, Russian Federation.

DISCLOSURE

CP declared having consultancy fees from AstraZeneca, Bristol Myers Squibb (BMS), Eisai, EUSA, Ipsen, Merck Serono, Merck Sharp & Dohme (MSD), Novartis, and Pfizer; stock from DNA; and research support from AstraZeneca, BMS, Eisai, EUSA, GE, Ipsen, Merck Serono, MSD, Novartis, and Pfizer; and CP was an expert witness for DNA. AB declared having received consultancy fees from BMS, MSD, Pfizer, and Roche; speaker honoraria from BMS and MSD; and research support from BMS and Pfizer. FRD declared having received research support from National Institutes of Health. MG declared having received speaker honoraria from General Electric. MAG declared having received consultancy fees from Abbvie, Alnylam, Amgen, Annexon, Appellis, Celgene, Janssen, Medscape, Physicians' Education Resource, Prothena, Research to Practice, Sanofi, and Spectrum; stock options from Aurora Bio; speaker honoraria from Akcea, Johnson and Johnson, and Teva; and research support from National Institutes of Health and Spectrum. JTK declared having received consultancy fees from Amgen and Vifor Pharma; stock from Chemocentryx; speaker honoraria from ExThera Medical and Vifor Pharma; and grants from ExThera Medical; and JTK was an expert witness in vaccine injury cases trialed at the US Federal Court of Claims. PT declared having received consultancy fees from AstraZeneca, Eli Lilly, Novartis, Pfizer, Pierre Fabre, and Roche; and speaker honoraria from AstraZeneca, Eli Lilly, Novartis, Pfizer, Pierre Fabre, and Roche. GW declared having received research support from the National Health and Medical Research Council. DCW declared having received consultancy fees from Amgen, Astellas, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Janssen, Mundipharma, Napp, and Vifor Fresenius Medical Care Renal Pharma; and speaker's honoraria from Amgen, Astellas, AstraZeneca, Mundipharma, Napp, Pharmacosmos, and Vifor Fresenius Medical Care Renal Pharma. WCW declared having consultancy fees from Akebia, Amgen, AstraZeneca, Bayer, Daiichi Sankyo, Relypsa, and Vifor Fresenius Medical Care Renal Pharma. JM declared having consultancy fees from Fresenius Medical Care and Vifor Pharma. All the other authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1. Staging of acute kidney injury.[33]

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