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Perspectives From an Onconephrology Interest Group: Conference Report

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Abstract

Introduction and objective: Onconephrology is a new and evolving field that deals with kidney complications in patients with cancer as well as the management of cancer in patients with preexisting kidney disease. With increasing numbers of patients with cancer with kidney-related complications, the field has garnered increased attention. Thus, an annual Greater Toronto Area Onconephrology Interest Group symposium was held in May 2019. The objective of the meeting was to demonstrate the junctures between oncology and nephrology by highlighting recent data regarding (1) kidney impairment in solid organ malignancies, (2) management and treatment of kidney cancer, (3) kidney impairment in hematologic malignancies, (4) malignancy and kidney transplantation, and (5) hyponatremia in patients with cancer.

Methods and sources of information: Through a structured presentation, the group explored key topics discussed at a Kidney Disease Improving Global Outcomes (KDIGO) Controversies Conference on Onconephrology. Expert opinions, clinical trial findings, and publication summaries were used to illustrate patient and treatment-related considerations in onconephrology.

Key findings: Kidney complications in patients with cancer are a central theme in onconephrology. An estimated 12% to 25% of patients with solid organ malignancies have chronic kidney disease (CKD), although in certain cancers, the prevalence of CKD is higher. Kidney impairment is also a common complication of some hematologic malignancies. The incidence of renal failure in patients with multiple myeloma is estimated at 18% to 56% and light chain cast nephropathy is seen in approximately 30% of these patients. In addition, there appears to be a bidirectional relationship between kidney cancer and CKD, with some data sets suggesting the risk increases as kidney function declines. Cancer is also of concern in patients with preexisting kidney disease. Kidney transplant recipients have a greater risk of cancer and a higher risk of cancer-related mortality. Kidney complications have also been associated with novel cancer therapies, such as immune checkpoint inhibitors and chimeric antigen receptor (CAR) T-cell therapy. An estimated 2% to 4% of patients initiating an immune checkpoint inhibitor may develop nephrotoxicity, whereas up to 40% of patients on CAR T-cell therapy experience cytokine release syndrome (CRS). Tumor lysis syndrome and electrolyte abnormalities, such as hyponatremia, have also been reported with CAR T-cell therapy. While the incidence and prevalence of hyponatremia vary depending on the cancer type and serum sodium cutoff point, hyponatremia may be seen in up to 46% of patients hospitalized in cancer centers.

Conclusions: Onconephrology is a developing field and the themes arising from this meeting indicate a need for greater collaboration between oncologists and nephrologists. Educational symposia and onconephrology fellowship programs may allow for improved cancer care for patients with kidney disease.

Abrégé

Contexte et objectifs: L'onconéphrologie est une discipline nouvelle et évolutive qui traite les complications néphrologiques chez les patients atteints d'un cancer et assure également la prise en charge des patients soignés en oncologie et présentant une néphropathie préexistante. En mai 2019, le symposium du *Greater Toronto Area Onconephrology Interest Group* a eu pour objectif de démontrer les points de jonction entre l'oncologie et la néphrologie en mettant en évidence les données récentes concernant : 1) l'insuffisance rénale en présence de tumeurs malignes touchant les organes solides; 2) la prise en charge et le traitement des cancers rénaux; 3) l'insuffisance rénale en présence de tumeurs malignes hématologiques; 4) la malignité et la transplantation rénale; et 5) l'hyponatrémie chez les patients atteints d'un cancer.

Sources et méthodologie: Par le biais d'une présentation structurée, le groupe s'est penché sur les thèmes clés discutés lors d'une conférence du KDIGO portant sur les controverses entourant l'onconéphrologie. Des avis d'experts, des résultats d'essais cliniques et des résumés de publications ont été utilisés pour illustrer les considérations relatives aux patients et aux traitements en onconéphrologie.

Principaux résultats: Les complications rénales chez les patients atteints d'un cancer sont un thème central en onconéphrologie. On estime qu'environ 12 à 25 % des patients présentant une tumeur maligne touchant les organes solides sont atteints d'insuffisance rénale chronique (IRC), bien que la prévalence soit plus élevée pour certains cancers. L'insuffisance rénale s'avère également une complication fréquente de certaines tumeurs malignes hématologiques. L'incidence d'IRC chez les patients atteints d'un myélome multiple est estimée entre 18 et 56 %, et une néphropathie à chaînes légères est observée chez environ 30 % de ces patients. En outre, on soupçonne l'existence d'une relation bidirectionnelle entre le cancer du rein et l'IRC; certains ensembles de données suggérant que le risque de cancer augmenterait avec le déclin de la fonction rénale. Le cancer est également préoccupant chez les patients ayant une néphropathie préexistante. Enfin, les receveurs d'une greffe rénale présentent un risque accru de cancer et de mortalité liée au cancer. Les complications rénales ont également été associées aux nouveaux traitements contre le cancer, comme les inhibiteurs du point de contrôle immunitaire et les thérapies par cellules CAR T. Environ 2 à 4 % des patients amorçant un traitement par les inhibiteurs de point de contrôle immunitaire pourraient développer une néphrotoxicité, alors que jusqu'à 40 % des patients traités par cellules CAR T présentent un syndrome de relargage de cytokines. Le syndrome de lyse tumorale et des anomalies électrolytiques, comme l'hyponatrémie, ont également été observés chez les patients traités par cellules CAR T. Bien que l'incidence et la prévalence de l'hyponatrémie varient en fonction du type de cancer et du seuil de natrémie, jusqu'à 46 % des patients hospitalisés dans les centres de cancérologie présentent cette anomalie.

Conclusion: L'onconéphrologie est une discipline en évolution et les thèmes issus de ce colloque soulignent le besoin d'accroître la collaboration entre les oncologues et les néphrologues. Les symposiums à caractère éducatif et les programmes de bourses d'études et de recherche en onconéphrologie pourraient améliorer les soins oncologiques prodigués aux patients atteints de néphropathies.

Keywords

cancer, chronic kidney disease, myeloma cast nephropathy, nephrotoxicity, onconephrology

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Introduction and Objective

Onconephrology is a relatively new and evolving field that deals with kidney complications in patients with cancer as well as the management of cancer in patients with preexisting kidney disease. The management of patients with cancer with kidney disease or treatment-related kidney injury, proteinuria, or electrolyte abnormalities is becoming increasingly complex to manage because of the wider use of newer and potentially nephrotoxic cancer therapies.[1] Moreover, the development of kidney complications in patients with cancer is associated with poor prognosis.[2] Therefore, prevention, early detection, long-term monitoring, and treatment of kidney complications in patients with cancer are of growing concern to oncologists and nephrologists.[3]

To discuss these challenges and demonstrate the junctures between oncology and nephrology, the fourth annual Greater Toronto Area Onco-nephrology Interest Group Symposium was convened. The group sought to provide educational updates on key topics in onconephrology: (1) kidney impairment in solid organ malignancies, (2) management and treatment of kidney cancer, (3) kidney impairment in hematologic malignancies, (4) malignancy and kidney transplantation, and (5) hyponatremia in patients with cancer.

Methods and Sources of Information

The fourth annual Greater Toronto Area Onco-nephrology Interest Group Symposium was held in May 2019, in Montreal, Canada. The meeting was chaired by Dr Paul Tam, Dr Bharat Nathoo, and Dr Christopher T. Chan.

Through a structured presentation by Dr Abhijat Kitchlu, meeting attendees reviewed the outcomes of discussions held at a Kidney Disease Improving Global Outcomes (KDIGO) Controversies Conference on Onconephrology in December 2018, in Milan, Italy. Expert opinions, clinical trial findings, and publication summaries shared by Dr Nelson Leung, Dr Sheldon Chen, and Dr Sheron Latcha were used to identify

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key management issues in nephrology relevant to patients with various types of malignancies—myeloma cast nephrology, hyponatremia, and chimeric antigen receptor (CAR) T-cell therapy.

Key Findings

Discussions at the annual Greater Toronto Area Onconephrology Interest Group Symposium focused on the relationship between kidney impairment and solid and hematologic malignancies, as well as adverse events related to the management of cancers.

Kidney Impairment and Solid Organ Malignancies

What is the epidemiology of chronic kidney disease in solid organ tumors? Based on data from multiple observational studies, it is estimated that 12% to 25% of patients with solid organ malignancies have chronic kidney disease (CKD), defined as an estimated glomerular filtration rate (eGFR) <60 mL/min at the time of treatment initiation. The rate is substantially higher in patients with genitourinary tract cancers such as renal cell carcinoma and bladder carcinoma, presumably due to loss of nephron mass, postrenal obstruction, and/or kidney-adverse therapies.[2,4-10]

To quantify the overall burden of acute kidney injury (AKI) among patients undergoing systemic cancer therapy, 163 071 Ontario patients initiating systemic cancer treatment between 2007 and 2014 were followed. A cumulative incidence of AKI, defined as a hospitalization for AKI or receipt of acute dialysis, of 9.3% was observed. This suggests that nearly 1 in 10 patients initiating cancer treatment in Ontario may have a clinically relevant episode of AKI. This may be related to the increased comorbidity and complexity of patients initiating cancer treatment and suggests a need for increased multidisciplinary collaboration to care for these patients.[11]

These findings are significant as reduced kidney function has been associated with worse cancer outcomes. In the largest study to date of this phenomenon, every 10 mL/min decline in kidney function was associated with an 18% increase in cancer-related mortality.[12]

What are the primary nephrotoxicities associated with novel cancer immunotherapies? Indications for immune checkpoint inhibitors (ICIs) are increasing and include common malignancies. These agents are humanized monoclonal antibodies that inhibit down-regulatory receptors on T cells (such as cytotoxic T-lymphocyte antigen 4 [CTLA-4] and programmed cell death 1 [PD-1] and its ligand [PD-L1]).[13] By blocking down-regulatory pathways ICI therapies allow T cells to remain activated and thereby enhance the antitumor immune response. However, despite benefits with respect to cancer outcomes, upregulation of the immune system has been associated with a wide spectrum of systemic immune-related adverse events.[14,15] Immune checkpoint inhibitor–associated immune-related adverse events have been reported with almost every organ system, including the kidneys, and nephrotoxicity has been estimated to occur in 2% to 4% of patients. The most frequently reported nephrotoxicity is acute interstitial nephritis (AIN), but others, including immune-mediated glomerular disease, have also been observed. However, it is currently unclear what factors specific to the patient, tumor, and/or therapy indicate which patients may develop nephrotoxicity.[14,16,17] A recent large, multicenter study involving 26 U.S. and Canadian sites assessed 138 patients with ICI-associated kidney injury (93% were AIN) and found that patients receiving concomitant proton pump inhibitor therapy and those receiving combination ICI treatment may be at elevated risk of AKI.[17] Currently, evidence for the management of ICI-associated nephrotoxicity remains limited. The American Society of Clinical Oncology (ASCO) guidelines for the management of immune-related adverse events recommend corticosteroids for ICI-related AIN (prednisone in the range of 1 mg/kg/d tapered over 4-6 weeks) along with cessation of the ICI.[18] In the aforementioned multicenter study, 86% of patients received corticosteroids with 40% and 45% achieving complete or partial recovery of AKI, respectively.[17]

The CAR T-cell therapy is another relatively novel cancer treatment approved in hematologic malignancies. The CAR T-cell therapy is associated with a significant immune response and cytokine release syndrome (CRS) has been reported in up to 40% of patients, with 25% developing cardiac dysfunction and vasodilatory shock. These patients may develop a prerenal AKI that can lead to acute tubular necrosis. Treatment is usually supportive but may also involve corticosteroid treatment and tocilizumab. The relationship between CAR T-cell therapy and nephrotoxicity is discussed in greater detail below.[19]

Under what circumstances is cancer screening indicated in dialysis patients? When it is indicated, which exams should be done and how often? Like milder forms of CKD, there are certain cancers for which dialysis patients may be at increased risk. Kidney and urinary tract cancers in particular have a higher incidence in end-stage kidney disease (ESKD) compared with the general population.[20] This increased risk must be balanced against the reduced overall life expectancy among dialysis patients, as well as decreased performance characteristics of screening tests in this population.[21-23] While more data are needed to confirm the benefits of screening the subset of dialysis patients with a longer life expectancy, cancer screening for transplant-eligible patients on dialysis is suggested. The screening recommendations are similar to those for the general population but include kidney imaging in patients on dialysis for >3 years.[24] However, there is, as of yet, minimal evidence to support this and screening approaches should be individualized to each patient.

Can we overcome underrepresentation of patients with CKD in cancer trials? A systematic review of more than 300 trials of

anticancer drugs published between 2012 and 2017 found that 85% of trials explicitly excluded patients based on kidney function. Most of these trials used a serum creatinine threshold to exclude patients and only 5% of trials used a preferred measure of kidney function estimation, such as eGFR. Most trials excluded patients with mild to moderate CKD (eGFR or CrCl <50 to 60 mL/min). Therefore, there is an urgent need for trials specifically focused on patients with impaired renal function.[25]

Management and Treatment of Kidney Cancer

Is CKD a risk factor and/or prognostic factor for renal cell carcinoma? The bidirectional relationship between kidney cancer and CKD is proposed to be a result of shared risk factors, including diabetic nephropathy, arteriosclerosis, hypertension, diabetes mellitus, and obesity, among others.[26]

A retrospective cohort study of 1 190 538 adults who had a measurement of kidney function obtained between 2000 and 2008 and had no prior cancer showed elevated cancer risk at CKD stage 3a. This risk increased with declining kidney function and reduced eGFR was associated with an independently higher risk of renal and urothelial cancer.[27]

Which patients are candidates for nephron-sparing surgery? While surgical resection remains the preferred treatment modality, nephrectomy has been recognized as an independent risk factor for kidney injury. In recent years, there has been a shift toward nephron-sparing procedures such as partial nephrectomy, thermal ablation, and active surveillance. Rates of AKI are similar across partial nephrectomy, thermal ablation, and radical nephrectomy.[28] However, progression to CKD is lower with partial nephrectomy and thermal ablation. Risk factors most strongly associated with the development of ESKD are older age, male sex, diabetes, and preoperative CKD.[29,30]

As such, European Society for Medical Oncology (ESMO) guidelines recommend partial nephrectomy in tumors <7 cm and in patients with impaired renal function. Radiofrequency, microwave, and cryoablation (with the aim of sparing nephron mass) have been included in the guidelines. In larger tumors, laparoscopic or open nephrectomy remains the recommended procedure.[31]

Kidney Impairment in Hematologic Malignancies

What renal pathologies are common in patients with multiple myeloma? Kidney failure is a common and serious consequence of multiple myeloma. The incidence of renal failure in patients with multiple myeloma has been reported to range from 18% to 56%. The most common cause of renal failure in these patients is light-chain cast nephropathy which is seen in approximately 30% of patients.[32]

Studies have shown that serum-free light-chain levels (sFLC) are predictive of the severity of renal impairment—as concentrations rise, so does the incidence of advanced or severe renal impairment, defined an eGFR <60 mL/min/1.73 m^2. This is significant as patients with multiple myeloma and severe renal impairment have a mortality risk that is ≥2 higher than patients with multiple myeloma and normal renal function. However, a reduction in sFLC by ≥50% in patients with multiple myeloma has been shown to improve acute renal function.[32,33] The speed at which sFLC reduction occurs is also important; sFLC reduction at day 21 is a significant predictor of renal recovery. One study found that for 80% of the population examined to recover, a reduction of 60% in sFLC was required by day 21.[34]

What evidence supports the use of bortezomib for myeloma cast nephropathy? Renal impairment in patients with multiple myeloma is correlated with a poor prognosis and efforts to ascertain sFLC-reducing strategies have been ongoing as the first report of plasmapheresis in a patient with multiple myeloma was published in 1976.[35]

The HOVON-65/GMMG-HD4 trial showed that a bortezomib-based regimen before and after autologous stem cell transplantation overcomes the negative prognostic impact of renal impairment in patients with multiple myeloma. The study examined 827 newly diagnosed myeloma patients who were randomized to receive 3 cycles of vincristine, adriamycin, dexamethasone (VAD) or bortezomib, adriamycin, dexamethasone (PAD) followed by autologous stem cell transplantation and maintenance with thalidomide (VAD-arm) or bortezomib every 2 weeks (PAD-arm). In patients with baseline creatinine ≥2 mg/dL, the renal response rate was 63% in the VAD-arm and 81% in the PAD-arm (P = .31). And while there was a high mortality rate within the first year, the overall survival at 3 years was 34% in the VAD-arm compared with 74% in the PAD-arm (P < .001).[36]

Is there a role for high cutoff dialysis in the management of multiple myeloma cast nephropathy? High cutoff (HCO) dialyzers use a large pore size with the intent of clearing higher molecular weight molecules and improving extracorporeal removal of sFLC. A small study (N = 19) was conducted to assess the effects of chemotherapy combined with HCO dialyzers on sFLC concentration and renal recovery in patients with myeloma cast nephropathy and dialysis-dependent acute renal failure. The study found that patients who received uninterrupted chemotherapy and extended HCO dialyzers experienced sustained reductions in sFLC concentrations and recovered independent renal function.[37]

Two recent randomized controlled trials, MYRE and EuLITE, have sought to compare HCO with conventional high-flux dialysis in patients with myeloma cast nephropathy.[38,39]

In both studies, HCO dialysis did not improve dialysis independence at 3 months (primary endpoint). The rate of hemodialysis independence in the MYRE trial was 41.3% in the HCO hemodialysis group vs 33.3% in the conventional hemodialysis group (P = .042); at 6 months, the rate was

56.5% (n = 26) vs 35.4% (n = 17), respectively (P = .04). In the EuLITE trial, outcomes in the HCO hemodialysis and conventional hemodialysis groups were comparable at 3 months—56% (n = 24) of patients in the HCO hemodialysis group and 51% (n = 24) of patients in the conventional hemodialysis group were independent from dialysis (P = .81). Moreover, there was no survival advantage with HCO hemodialysis in the MYRE trial and a lower overall survival rate with HCO hemodialysis in the EuLITE trial.[38,39]

Critics were therefore quick to dismiss the potential benefits of HCO dialyzers; however, the authors of this publication believe that further consideration is required. Analysis of the MYRE and EuLITE trials, specifically the trial designs and hematologic responses, may explain the lack of effect observed with HCO dialyzers.

In the EuLITE trial, patients received HCO hemodialysis for 6 hours on day 0 and 8 hours on days 2, 3, 5 to 7, 9, and 10. After day 12, patients received 8 hours of HCO hemodialysis on alternate days, and from day 21 onward, HCO hemodialysis was given for 6 hours 3 times a week. Sixty grams of serum albumin was administered during the last hour of each dialysis. Patients in the EuLITE trial also received a regimen comprising modified bortezomib, doxorubicin, and dexamethasone. In the MYRE trial, eight 5-hour hemodialysis sessions were planned over the first 10 days, and, if needed, patients received 3 additional weekly hemodialysis sessions. A postdialysis perfusion of 20 g of albumin was administered if serum albumin was <25 g/L prior to dialysis. Forty-one percent of the HCO hemodialysis sessions and 4% of the conventional hemodialysis sessions required postdialysis perfusion of albumin. Patients in the MYRE trial also received bortezomib and dexamethasone, and cyclophosphamide as of cycle 3.[38,39]

Doxorubicin, administered in the EuLITE, but not the MYRE trial, is 74% to 76% bound to plasma protein and has a terminal half-life of 20 to 48 hours.[38-40] One may hypothesize that given the need to administer serum albumin, doxorubicin was dialyzed, thus reducing the hematological efficacy observed. This theory is supported by studies of patients receiving bortezomib and dexamethasone, in which rates of very good partial response were similar to those reported in EuLITE.[41,42] Moreover, patients who received HCO dialysis in EuLITE more frequently had chemotherapy interruption (infection due to antibiotic removal) which may have decreased the response to therapy and increased the observed rate of mortality.[39]

The longer HCO hemodialysis performed in the EuLITE trial may potentially have been associated with a poorer hematologic response and overall survival as a result of decreased the efficacy of doxorubicin, and dexamethasone, increased risk of infection, and increased chemotherapy disruption.

In addition, when considering survival in patients with myeloma with renal failure, early mortality is common.[36,43-45] In the MYRE trial, 20% (n = 9) of patients in the HCO hemodialysis group and 21% (n = 10) in the conventional hemodialysis group had died at 12 months. However, at 3 months, no deaths were recorded in the HCO hemodialysis group.[38] Thus, the hematologic response observed in the MYRE trial may have been a function of the benefits of HCO hemodialysis.

What is CAR T-cell therapy and what are the risks associated with its use? The CAR T-cell therapy is a rapidly evolving form of immunotherapy known as adoptive cell transfer. The transferred T cells are genetically engineered to express a CAR that recognizes surface antigens, linked to an intracellular costimulatory domain (CD28 or 4-1BB) and signaling domain to amplify the immune response against tumor cells. When targeted to tumor surface antigens, CAR T cells kill tumor cells on antigen recognition.[19,46]

Food and Drug Administration–approved CAR T-cell therapies are tisagenlecleucel (Kymriah) for children and adolescents with acute lymphocytic leukemia and axicabtagene ciloleucel (Yescarta) to treat adults with various forms of large B-cell lymphoma. However, while CAR T-cell therapies have focused on hematologic malignancies, they are being increasingly studied in solid cancers. There are now more than 200 clinical trials investigating CAR T cells for both hematologic and solid tumors.[19,46] Given their increasing use, it is important to understand the potential adverse effects, including to the kidney, that may be encountered with CAR T cells.

Cytokine release syndrome, a systemic inflammatory response that on activation of CAR T cells, is among the most frequent serious adverse events and cause of morbidity following CAR T-cell therapy. While CRS was rarely observed in studies of first-generation CAR T-cell constructs, it is more common with second-generation CAR constructs that have additional costimulatory signaling domains. The risk of CRS is influenced by not only the type of therapy, but also the underlying disease and patient characteristics. The CRS after CAR T-cell therapy that presents with fever, hypotension, coagulopathy, and capillary leak and has been reported to occur in 54% to 91% of patients.[47,48]

Chimeric antigen receptor T-cell therapy may also induce nephrotoxicity. The capillary leak associated with severe CRS can result in prerenal physiology, and the high fever and vomiting that accompany CRS may cause intravascular volume depletion. Cytokine release syndrome–related acute cardiomyopathy can also further exacerbate kidney hypoperfusion, which can lead to AKI. Acute kidney injury may also result from tumor lysis syndrome (TLS) in patients with large tumor burdens who are treated with CAR T-cell therapy. Intratubular uric acid and calcium-phosphate crystal precipitation triggered by the cytokine storm that occurs with TLS can trigger AKI and result in additional kidney injury.[49]

Other serious adverse events related to CAR T-cell therapy include cytokine-related encephalopathy and hemophagocytic lymphohistiocytosis.[50] Hypokalemia (47%),

hypophosphatemia (37%), and hyponatremia (5%) have also been reported with CAR T-cell therapy.[49]

Prevention and treatment of CAR T-cell complications include chemotherapy to decrease the tumor burden and steroids to dampen inflammation. Intravenous (IV) fluid resuscitation and vasopressors to maintain systemic hemodynamics and renal perfusion may also be prescribed. Tocilizumab, an anti–IL-6 receptor antibody, is indicated for severe grade 3/4 CRS and may be used in conjunction with corticosteroids for patients with recurrent symptoms.[49]

How do we recognize and treat TLS? There is a high incidence of TLS in hematological cancers. Tumor lysis syndrome can lead to acute renal failure and be life-threatening. Early recognition of high-risk patients and initiation of therapy is therefore important.[51]

The 2004 Cairo-Bishop definition of clinical TLS is either a 25% change or level above or below normal, for any 2 or more serum values of uric acid, potassium, phosphate, and calcium within 3 days before or 7 days after the initiation of chemotherapy, and creatinine $\geq$1.5 upper limit of normal, cardiac arrhythmia/sudden death, or seizure. Of note, this definition employs a creatinine criterion that differs from other definitions, such as KDIGO.[51,52]

Tumor lysis syndrome risk assessment should be based on cancer type, patient/laboratory parameters, and therapy. The use of potent, novel agents, such as venetoclax (currently used in chronic lymphocytic leukemias and acute myeloid leukemias), may represent risk factors for TLS and should be incorporated into risk stratification and prophylaxis.[53] The mainstays of TLS prophylaxis and treatment include hydration and diuresis, control of hyperuricemia with allopurinol prophylaxis and rasburicase treatment, and vigilant monitoring of electrolyte abnormalities. Febuxostat is recommended only for patients unable to receive allopurinol and do not have access to rasburicase.[51,54]

Malignancy and Kidney Transplantation

What are the incidence, cancer risk factors, and mortality rates of cancers in kidney transplant recipients compared with the general population? Transplant recipients are known to have an increased incidence of cancer after transplantation compared with the general population. After kidney transplantation, patients are at a >2.5-fold greater risk of cancer death than the age- and sex-matched general population. The increased overall cancer risk seen in kidney transplant recipients is primarily driven by a higher rate of immune-related cancers, including nonmelanoma skin cancer, posttransplant lymphoproliferative disorder, and anogenital cancers. The risk appears to increase considerably with time since transplant.[55,56]

Should cancer screening differ from the general population? Despite recommendations for routine screening, the uptake of screening remains low in transplant recipients. In Ontario, screening rates for cervical cancer and breast cancer were found to be much lower in kidney transplant recipients than those in the general population. Because early detection through cancer screening may modify the longer term cancer prognoses, kidney transplant patients should be encouraged to undertake routine screening and a proactive approach to preventive health care. Moreover, the lower rates of screening represent a missed opportunity to improve patient care.[56,57]

Hyponatremia in Patients With Cancer

What are the frequency and consequences of hyponatremia in patients with cancer? Hyponatremia, defined as serum sodium <135 mmol/L, is a common electrolyte abnormality affecting up to 46% of patients hospitalized in cancer centers.[58,59]

Acute hyponatremia is common in hospitalized patients receiving IV hypotonic solutions.[60] Serious neurological complications may occur following large or rapid declines in serum sodium, including seizures, coma, respiratory arrest, or brainstem herniation. In cases of acute hyponatremia, the rate of cellular swelling can overtake the brain's ability to regulate volume, resulting in cerebral edema. The risk of death during hospitalization is increased by >50% in patients admitted with hyponatremia compared with normonatremia.[61,62]

Hyponatremia treatment should aim to raise serum sodium at the rate at which it fell. Treatment must be careful and deliberate, with the correction made over an appropriate time frame; osmotic demyelination syndrome can occur if the correction is made too quickly.[60]

What variables should be included in calculations of fluid administration rate? Many formulae have been developed to evaluate and correct hyponatremia. Most recent formulae are derived from the Edelman equation, which describes the variables that correlate best with serum sodium concentrations.[63] However, there are 2 important limitations to the Edelman equation—failure to incorporate changing sodium levels and time.

Edelman equation:

$$\text{Plasma water sodium concentration} = \frac{(\text{total exchangeable sodium}) + (\text{total exchangeable potassium})}{\text{total body water}}$$

The newer Chen-Shey equation takes into consideration not only the change in sodium that is desired or anticipated, but also the timeframe over which this change should occur (ie, the rate of sodium correction). This makes the equation practical, allowing a clinician to choose the desired rate of sodium correction that will avoid osmotic demyelination and then calculate the IV fluid rate required to achieve this rate.[58]

To use the Chen-Shey equation, users input baseline data on the input and output rates of sodium, potassium, water,

Table 1. Summary of Key Insights and Data.

Kidney impairment and solid organ malignancies	An estimated 12%-25% of patients with solid organ malignancies have CKD. However, in certain cancers, such as genitourinary tract cancers, the prevalence of CKD is higher.[2,4-10]
	An estimated 2%-4% of patients initiating an immune checkpoint inhibitor may develop nephrotoxicity, most commonly acute interstitial nephritis. Up to 40% of patients on CAR T-cell therapy experience CRS. TLS and electrolyte abnormalities have also been reported with CAR T-cell therapy.[14,16,17,19]
	The screening approach should be individualized and based on patient values, life expectancy, and transplant eligibility. Among those appropriate for screening, cancer screening recommendations are similar to general population screening guidelines, but include kidney imaging in patients on dialysis for >3 years.[24]
	An estimated 85% of trials published between 2012 and 2017 explicitly excluded patients based on kidney function. There is an urgent need for trials specifically focused on patients with impaired renal function.[25]
Management and treatment of kidney cancer	There appears to be a bidirectional relationship between kidney cancer and CKD. Some data sets suggest the risk increases as kidney function declines, although the underlying mechanisms are unclear.[26]
	The 2019 European Society for Medical Oncology clinical practice guidelines recommend partial nephrectomy in smaller tumors and patients with impaired renal function.[31]
Kidney impairment in hematologic malignancies	The incidence of renal failure in patients with multiple myeloma is estimated at 18%-56%. Light chain cast nephropathy is seen in approximately 30% of these patients.[32]
	Among patients with myeloma cast nephropathy receiving bortezomib-based chemotherapy, high cutoff hemodialysis vs conventional high-flux did not improve dialysis independence at 3 months in the MYRE and EuLITE trials.[38,39] Analysis of the study designs and hematologic responses, may explain the lack of effect observed.
	CRS is among the most common serious adverse events and cause of morbidity following CAR T-cell therapy. The capillary leak associated with severe CRS can result in prerenal physiology and CRS-related acute cardiomyopathy can exacerbate kidney hypoperfusion and lead to acute kidney injury.[49]
	The risk of TLS is determined by tumor type, patient characteristics, and type of therapy. Allopurinol and rasburicase are the 2 main treatments for addressing uric acid in TLS. Febuxostat may be an alternative in some patients.[51]
Malignancy and kidney transplantation	Kidney transplant recipients have a greater risk of cancer and a higher risk of cancer-related mortality.[55]
	As cancer-related mortality rates are high in solid-organ transplant recipients, increased screening and treatment strategies may be needed.[56]
Hyponatremia in onconephrology	While the incidence and prevalence of hyponatremia vary depending on the cancer type and serum sodium cutoff point, hyponatremia may be seen in up to 46% of patients hospitalized in cancer centers. While some patients are asymptomatic, hyponatremia may result in neurological symptoms, especially when serum sodium declines rapidly or by a substantial amount.[58,61]
	The Chen-Shey equation also includes changes in sodium levels and time, allowing clinicians to determine the intravenous fluid rate needed to achieve a specific rate of change of sodium concentration.[58]

Note. CKD: chronic kidney disease; CAR = chimeric antigen receptor; CRS = cytokine release syndrome; TLS: tumor lysis syndrome.

predicted urine sodium and potassium, flow rate, and the patient's body weight. They state how quickly the target sodium level should be reached, whether the patient is on IV fluids or salt tablets, and if there is a preferred treatment. The Chen-Shey equation then returns the infusion rate required to reach the targeted sodium level and urine sodium level. If and when variables change, the equation can be recalculated with the new values.[58]

Conclusions

Onconephrology is a broad new specialty that encompasses kidney complications in solid and hematologic patients with cancer, as well as the management of cancer in patients with preexisting kidney disease. It is an evolving field and additional trials are needed to understand the mechanisms underlying kidney-related complications in these patients. Further studies will elucidate the kidney risks associated with novel cancer therapies, as well as strategies for cancer treatment in the population with existing kidney disease.

With a bidirectional relationship between kidney disease and cancer, the growing intersection of patients with cancer and kidney issues will offer new challenges to oncologists and nephrologists. The themes arising from the annual Greater Toronto Area Onco-nephrology Interest Group Symposium indicate a need for greater collaboration between oncologists and nephrologists (Table 1). Educational symposia and onconephrology fellowship programs may allow for improved cancer care for patients with kidney disease.

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References

1. Abudayyeh AA, Lahoti A, Salahudeen AK. Onconephrology: the need and the emergence of a subspecialty in nephrology. *Kidney Int*. 2014;85(5):1002-1004. doi:10.1038/ki.2014.29.
2. Launay-Vacher V. Epidemiology of chronic kidney disease in cancer patients: lessons from the IRMA study group. *Semin Nephrol*. 2010;30(6):548-556. doi:10.1016/j.semnephrol.2010.09.003.
3. KDIGO. Controversies Conference on Onco-Nephrology—KDIGO. https://kdigo.org/conferences/onco-nephrology-conference/. Accessed March 27, 2020.
4. Launay-Vacher V, Oudard S, Janus N, et al. Prevalence of Renal Insufficiency in cancer patients and implications for anticancer drug management. *Cancer*. 2007;110(6):1376-1384. doi:10.1002/cncr.22904.
5. Janus N, Launay-vacher V, Byloos E, et al. Cancer and renal insufficiency results of the BIRMA study. *Br J Cancer*. 2010;103(12):1815-1821. doi:10.1038/sj.bjc.6605979.
6. Canter D, Kutikov A, Manley B, et al. Utility of the R.E.N.A.L.-nephrometry scoring system in objectifying treatment decision-making of the enhancing renal mass. *Urology*. 2011;78(5):1089-1094. doi:10.1016/j.urology.2011.04.035.
7. Nakamura Y, Tsuchiya K, Nitta K, Ando M. [Prevalence of anemia and chronic kidney disease in cancer patients: clinical significance for 1-year mortality]. *Nihon Jinzo Gakkai Shi*. 2011;53(1):38-45.
8. da Costa E, Silva VT, Costalonga EC, Coelho FO, Caires RA, Burdmann EA. Assessment of kidney function in patients with cancer. *Adv Chronic Kidney Dis*. 2018;25(1):49-56. doi:10.1053/j.ackd.2017.10.010.
9. Lane BR, Demirjian S, Derweesh IH, et al. Survival and functional stability in chronic kidney disease due to surgical removal of nephrons: importance of the new baseline glomerular filtration rate. *Eur Urol*. 2015;68(6):996-1003. doi:10.1016/j.eururo.2015.04.043.
10. Eisenberg MS, Thompson RH, Frank I, et al. Long-term renal function outcomes after radical cystectomy. *J Urol*. 2014;191(3):619-625. doi:10.1016/j.juro.2013.09.011.
11. Kitchlu A, McArthur E, Amir E, et al. Acute kidney injury in patients receiving systemic treatment for cancer: a population-based cohort study. *JNCI J Natl Cancer Inst*. 2019;111(7):727-736. doi:10.1093/jnci/djy167.
12. Iff S, Craig JC, Turner R, et al. Reduced estimated GFR and cancer mortality. *Am J Kidney Dis*. 2014;63(1):23-30. doi:10.1053/j.ajkd.2013.07.008.
13. Weber J. Immune checkpoint proteins: a new therapeutic paradigm for cancer—preclinical background: CTLA-4 and PD-1 blockade. *Semin Oncol*. 2010;37(5):430-439. doi:10.1053/j.seminoncol.2010.09.005.
14. Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. *N Engl J Med*. 2018;378:158-168. doi:10.1056/NEJMra1703481
15. Abdel-Wahab N, Shah M, Lopez-Olivo MA, Suarez-Almazor ME. Use of immune checkpoint inhibitors in the treatment of patients with cancer and preexisting autoimmune disease: a systematic review. *Ann Intern Med*. 2018;168(2):121-130. doi:10.7326/M17-2073.
16. Sury K, Perazella MA, Shirali AC. Cardiorenal complications of immune checkpoint inhibitors. *Nat Rev Nephrol*. 2018;14(9):571-588. doi:10.1038/s41581-018-0035-1.
17. Cortazar FB, Marrone KA, Troxell ML, et al. Clinicopathological features of acute kidney injury associated with immune checkpoint inhibitors. *Kidney Int*. 2016;90(3):638-647. doi:10.1016/j.kint.2016.04.008.
18. Brahmer JR, Lacchetti C, Schneider BJ, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol off J Am Soc Clin Oncol*. 2018;36(17):1714-1768. doi:10.1200/JCO.2017.77.6385.
19. Jhaveri KD, Rosner MH. Chimeric antigen receptor T cell therapy and the kidney: what the nephrologist needs to know. *Clin J Am Soc Nephrol*. 2018;13(5):796-798. doi:10.2215/CJN.12871117.
20. Butler AM, Olshan AF, Kshirsagar AV, et al. Cancer incidence among US Medicare ESRD patients receiving hemodialysis, 1996-2009. *Am J Kidney Dis*. 2015;65(5):763-772. doi:10.1053/j.ajkd.2014.12.013.
21. Saran R, Robinson B, Abbott KC, et al. US renal data system 2018 annual data report: epidemiology of kidney disease in the United States. *Am J Kidney Dis off J Natl Kidney Found*. 2019;73(3 suppl 1):A7-A8. doi:10.1053/j.ajkd.2019.01.001.
22. Castellanos MR, Paramanathan K, El-Sayegh S, Forte F, Buchbinder S, Kleiner M. Breast cancer screening in women with chronic kidney disease: the unrecognized effects of metastatic soft-tissue calcification. *Nat Clin Pract Nephrol*. 2008;4(6):337-341. doi:10.1038/ncpneph0804.
23. Bruun L, Björk T, Lilja H, Becker C, Gustafsson O, Christensson A. Percent-free prostate specific antigen is elevated in men on haemodialysis or peritoneal dialysis treatment. *Nephrol Dial Transplant*. 2003;18(3):598-603. doi:10.1093/ndt/18.3.598.
24. Scherer JS, Holley JL. The role of time-limited trials in dialysis decision making in critically ill patients. *Clin J Am Soc Nephrol*. 2016;11(2):344-353. doi:10.2215/CJN.03550315.
25. Kitchlu A, Shapiro J, Amir E, et al. Representation of patients with chronic kidney disease in trials of cancer therapy. *JAMA*. 2018;319(23):2437-2439. doi:10.1001/jama.2018.7260.
26. Li L, Lau WL, Rhee CM, et al. Risk of chronic kidney disease after cancer nephrectomy. *Nat Rev Nephrol*. 2014;10(3):135-145. doi:10.1038/nrneph.2013.273.
27. Lowrance WT, Ordoñez J, Udaltsova N, Russo P, Go AS. CKD and the risk of incident cancer. *J Am Soc Nephrol*. 2014;25(10):2327-2334. doi:10.1681/ASN.2013060604.
28. Patel HD, Pierorazio PM, Johnson MH, et al. Renal functional outcomes after surgery, ablation, and active surveillance of localized renal tumors: a systematic review and meta-analysis.

Clin J Am Soc Nephrol. 2017;12(7):1057-1069. doi:10.2215/CJN.11941116.
29. Chapman D, Moore R, Klarenbach S, Braam B. Residual renal function after partial or radical nephrectomy for renal cell carcinoma. *Can Urol Assoc J*. 2010;4(5):337-343.
30. Ellis RJ, Edey DP, Vecchio SJD, et al. End-stage kidney disease following surgical management of kidney cancer. *Clin J Am Soc Nephrol*. 2018;13(11):1641-1648. doi:10.2215/CJN.06560518.
31. Escudier B, Porta C, Schmidinger M, et al. Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. *Ann Oncol*. 2019;30(5):706-720. doi:10.1093/annonc/mdz056.
32. Leung N, Gertz MA, Zeldenrust SR, et al. Improvement of cast nephropathy with plasma exchange depends on the diagnosis and on reduction of serum free light chains. *Kidney Int*. 2008;73(11):1282-1288. doi:10.1038/ki.2008.108.
33. Yadav P, Cockwell P, Cook M, et al. Serum free light chain levels and renal function at diagnosis in patients with multiple myeloma. *BMC Nephrol*. 2018;19(1):178. doi:10.1186/s12882-018-0962-x.
34. Hutchison CA, Cockwell P, Stringer S, et al. Early reduction of serum-free light chains associates with renal recovery in myeloma kidney. *J Am Soc Nephrol*. 2011;22(6):1129-1136. doi:10.1681/ASN.2010080857.
35. Feest TG, Burge PS, Cohen SL. Successful treatment of myeloma kidney by diuresis and plasmaphoresis. *Br Med J*. 1976;1(6008):503-504.
36. Scheid C, Sonneveld P, Schmidt-Wolf IGH, et al. Bortezomib before and after autologous stem cell transplantation overcomes the negative prognostic impact of renal impairment in newly diagnosed multiple myeloma: a subgroup analysis from the HOVON-65/GMMG-HD4 trial. *Haematologica*. 2014;99(1):148-154. doi:10.3324/haematol.2013.087585
37. Hutchison CA, Bradwell AR, Cook M, et al. Treatment of acute renal failure secondary to multiple myeloma with chemotherapy and extended high cut-off hemodialysis. *Clin J Am Soc Nephrol*. 2009;4(4):745-754. doi:10.2215/CJN.04590908.
38. Bridoux F, Carron P-L, Pegourie B, et al. Effect of high-cutoff hemodialysis vs conventional hemodialysis on hemodialysis independence among patients with myeloma cast nephropathy: a randomized clinical trial. *JAMA*. 2017;318(21):2099-2110. doi:10.1001/jama.2017.17924.
39. Hutchison CA, Cockwell P, Moroz V, et al. High cut-off versus high-flux haemodialysis for myeloma cast nephropathy in patients receiving bortezomib-based chemotherapy (EuLITE): a phase 2 randomised controlled trial. *Lancet Haematol*. 2019;6(4):e217-e228. doi:10.1016/S2352-3026(19)30014-6.
40. PubChem. Doxorubicin. https://pubchem.ncbi.nlm.nih.gov/compound/31703. Accessed April 7, 2020.
41. Harousseau JL, Attal M, Leleu X, et al. Bortezomib plus dexamethasone as induction treatment prior to autologous stem cell transplantation in patients with newly diagnosed multiple myeloma: results of an IFM phase II study. *Haematologica*. 2006;91(11):1498-1505.
42. Harousseau J-L, Attal M, Avet-Loiseau H, et al. Bortezomib plus dexamethasone is superior to vincristine plus doxorubicin plus dexamethasone as induction treatment prior to autologous stem-cell transplantation in newly diagnosed multiple myeloma: results of the IFM 2005-01 phase III trial. *J Clin Oncol*. 2010;28(30):4621-4629. doi:10.1200/JCO.2009.27.9158.
43. Ludwig H, Bolejack V, Crowley J, et al. Survival and years of life lost in different age cohorts of patients with multiple myeloma. *J Clin Oncol*. 2010;28(9):1599-1605. doi:10.1200/JCO.2009.25.2114.
44. Dimopoulos MA, Stewart AK, Masszi T, et al. Carfilzomib-lenalidomide-dexamethasone vs lenalidomide-dexamethasone in relapsed multiple myeloma by previous treatment. *Blood Cancer J*. 2017;7(4):e554. doi:10.1038/bcj.2017.31.
45. Clark WF. Correction: plasma exchange when myeloma presents as acute renal failure. *Ann Intern Med*. 2007;146(6):471. doi:10.7326/0003-4819-146-6-200703200-00024.
46. Hartmann J, SchÃ¼ÃŸler-Lenz M, Bondanza A, Buchholz CJ. Clinical development of CAR T cells-challenges and opportunities in translating innovative treatment concepts. *EMBO Mol Med*. 2017;9(9):1183-1197. doi:10.15252/emmm.201607485.
47. Hay KA, Hanafi L-A, Li D, et al. Kinetics and biomarkers of severe cytokine release syndrome after CD19 chimeric antigen receptor–modified T-cell therapy. *Blood*. 2017;130(21):2295-2306. doi:10.1182/blood-2017-06-793141.
48. Shimabukuro-Vornhagen A, Gödel P, Subklewe M, et al. Cytokine release syndrome. *J Immunother Cancer*. 2018;6(1):56. doi:10.1186/s40425-018-0343-9.
49. Perazella MA, Shirali AC. Nephrotoxicity of cancer immunotherapies: past, present and future. *J Am Soc Nephrol*. 2018;29(8):2039-2052. doi:10.1681/ASN.2018050488.
50. Neelapu SS, Tummala S, Kebriaei P, et al. Chimeric antigen receptor T-cell therapy—assessment and management of toxicities. *Nat Rev Clin Oncol*. 2018;15(1):47-62. doi:10.1038/nrclinonc.2017.1480.
51. Cairo MS, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification. *Br J Haematol*. 2004;127(1):3-11. doi:10.1111/j.1365-2141.2004.05094.x.
52. KDIGO. Section 2: AKI Definition. Elsevier Enhanced Reader. doi:10.1038/kisup.2011.32.
53. Rastegar M, Kitchlu A, Shirali AC. Onco-nephrology. In: Finkel K, Perazella MA, Cohen E, eds. *Onco-nephrology e-book*.1st ed. Elsevier. https://www.elsevier.ca/ca/product.jsp?isbn=9780323549615. Published 2019. Accessed May 5, 2020.
54. Spina M, Nagy Z, Ribera JM, et al. FLORENCE: a randomized, double-blind, phase III pivotal study of febuxostat versus allopurinol for the prevention of tumor lysis syndrome (TLS) in patients with hematologic malignancies at intermediate to high TLS risk. *Ann Oncol*. 2015;26(10):2155-2161. doi:10.1093/annonc/mdv317.
55. Au EH, Chapman JR, Craig JC, et al. Overall and site-specific cancer mortality in patients on dialysis and after kidney transplant. *J Am Soc Nephrol*. 2019;30:471-480. doi:10.1681/ASN.2018090906
56. Acuna SA, Fernandes KA, Daly C, et al. Cancer mortality among recipients of solid-organ transplantation in Ontario, Canada. *JAMA Oncol*. 2016;2(4):463-469. doi:10.1001/jamaoncol.2015.5137.
57. Wong G, Hayward JS, McArthur E, et al. Patterns and predictors of screening for breast and cervical cancer in women with

CKD. *Clin J Am Soc Nephrol*. 2017;12(1):95-104. doi:10.2215/CJN.05990616.
58. Chen S, Shey J. Kinetic sodium equation with built-in rate of correction: aid to prescribing therapy for hyponatremia or hypernatremia. *J Onco-Nephrol*. 2017;1(3):204-212. doi:10.5301/jo-n.5000023.
59. Lee JJY, Kilonzo K, Nistico A, Yeates K. Management of hyponatremia. *CMAJ*. 2014;186:E281-E286. doi:10.1503/cmaj.120887
60. Palmer BF, Clegg DJ. Hyponatremia in the cancer patient. *J Onco-Nephrol*. 2017;1(2):87-94. doi:10.5301/jo-n.5000007.
61. Castillo JJ, Vincent M, Justice E. Diagnosis and management of hyponatremia in cancer patients. *The Oncologist*. 2012;17(6):756-765. doi:10.1634/theoncologist.2011-0400
62. Waikar SS, Mount DB, Curhan GC. Mortality after hospitalization with mild, moderate, and severe hyponatremia. *Am J Med*. 2009;122(9):857-865. doi:10.1016/j.amjmed.2009.01.027.
63. Edelman IS, Leibman J, O'meara MP, Birkenfeld LW. Interrelations between serum sodium concentration, serum osmolarity and total exchangeable sodium, total exchangeable potassium and total body water. *J Clin Invest*. 1958;37(9):1236-1256.