Onconephrology: The Latest Frontier in the War against Kidney Disease

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ABSTRACT

Renal diseases in patients with cancer have many unique features, and often these diseases require specialized approaches. Newer cancer therapy has increased cancer cure rate and survival time, but such benefit is not fully realized, partly because of therapy-associated toxicities. Fluid and electrolyte abnormalities are very common in patients with cancer, as are acute and chronic kidney injury. With the evolving complexities of newer cancer therapies, a comprehensive team approach is becoming necessary. It is essential for nephrologists to be informed and involved in cancer care. Many nephrologists caring for patients with cancer in the United States have recently met and formed a focus group, the OncoNephrology Forum, under the American Society of Nephrology. This update addresses what is clinically unique about onconephrology, the objectives and functions of the newly formed forum, and the potential of onconephrology becoming a subspecialty in nephrology.


The association between kidney disease and cancer has been long recognized, and indeed certain clinical entities, such as the syndrome of inappropriate antidiuretic hormone and tumor lysis syndrome, have close associations with cancer.1,2 With the wider use of chemotherapeutic conditioning regimens and stem cell transplantation, and the introduction of many targeted therapies, the link between kidney disease and cancer has unfortunately become stronger. Not only is cancer often associated with abnormalities that affect the kidney, but cancer therapy often leads to both acute and chronic kidney injury.3 Furthermore, the marked improvements in cancer therapy have led to increasing numbers of cancer survivors, many of them with residual kidney injury.4,5 For instance, anti–vascular endothelial growth factor (VEGF) therapy is associated with increased incidence of hypertension, proteinuria, and CKD.6 A better understanding of the renal complications of anti-VEGF therapy has also led to greater understanding of the functioning of the glomerular filter and the pathogenesis of preeclampsia.7,8 As with anti-VEGF therapy, newer myeloma therapies have also increased survival of patients with CKD.9,10 Thus, these welcoming new advances in cancer management present newer opportunities as well as challenges for the nephrology community. A better understanding of the rapidly evolving field of cancer biology and cancer therapy is required for nephrologists to become a valuable member of the cancer care team, rendering the best nephrology care possible. Recently, several nephrologists caring for patients with cancer in the United States have met and formed a focus group, the OncoNephrology Forum (ONF), under the American Society of Nephrology. In this clinical update we discuss what is clinically unique about onconephrology, the objective and function of the newly formed ONF, and the potential evolution of onconephrology as a subspecialty of nephrology.

UNIQUE FEATURES OF NEPHROLOGIC DISORDERS IN CANCER

AKI Burden in Cancer

AKI is probably the most common form of renal disease for which a nephrologist would be consulted in a hospitalized patient with cancer. The limited epidemiologic data on AKI in patients with cancer suggest that the incidence is at least threefold higher in these patients than those without cancer.4,11–13 The cause of AKI in hospitalized patients with cancer suggest that the incidence is at least threefold higher in these patients than those without cancer.4,11–13 The cause of AKI in hospitalized patients with cancer is almost always multifactorial, with hypovolemia, sepsis, and toxic drugs often contributing concomitantly.14,15 A higher rate of AKI in patients with cancer is not surprising given the effects of cancer or cancer therapy on several factors that cause AKI, such as volume...
depletion, increased propensity to develop contrast nephropathy, tumor lysis syndrome, abnormal uric acid homeostasis, hypercalcemia, myeloma and myeloma kidney, direct parenchymal involvement of the tumor, intense chemotherapy protocols often involving nephrotoxic drugs, stem cell transplants with immunosuppression leading to sepsis, veno-occlusive disease, graft versus host disease, thrombotic microangiopathy, and a variety of additional causes and mechanisms.\textsuperscript{16–23} Furthermore, cancer therapy is increasingly available to elderly patients, a subpopulation that is particularly vulnerable to nephrotoxic drugs and intravenous contrast media.\textsuperscript{24}

The list of potentially nephrotoxic drugs used in patients with cancer, especially after stem cell transplantation, is long, and often includes several well known unavoidable nephrotoxins, such as platinum compounds, methotrexate, anti-VEGF agents, calcineurin inhibitors, aminoglycosides, colistin, acyclovir, amphotericin, cidofovir, and bisphosphonates.\textsuperscript{3} It is well known that several chemotherapeutic agents can lead to AKI, but what is less well known is that reduced renal function (whether from the chemotherapeutic agents themselves or from other mechanisms, such as volume depletion) can initiate a vicious cycle (Figure 1). Kidney failure leads to higher systemic chemotherapeutic levels that result in neutropenic sepsis, multiorgan failure, and death. Therefore, optimizing the renal status of the patient before chemotherapy, such as by correcting volume status, removing potential nephrotoxic agents, and taking precautionary measures against tumor lysis, can reduce the chance for AKI and chemotoxicity risks.

Patients receiving outpatient chemotherapy are at higher risk for prerenal AKI, but the risk is reduced in patients receiving in-home intravenous fluid. A recent analysis of 3560 patients admitted to the University of Texas M.D. Anderson Cancer Center (MDACC) in Houston over 3 months revealed an incidence rate of AKI of 14.5% according to the Acute Kidney Injury Network criteria, a rate threefold higher than that in the non-cancer setting.\textsuperscript{4,25} This and other studies also report poor clinical outcomes in patients with cancer who develop AKI in the hospital.\textsuperscript{13,20} Dialysis was required in 10% of these patients, and nearly 30%–40% of oligoanuric patients requiring dialysis had to be treated with continuous renal replacement treatment because of severe septic shock, fluid overload, or tumor lysis syndrome.\textsuperscript{15} The experience from MDACC also shows that sustained low-efficiency dialysis in the continuous mode simplifies continuous renal replacement therapy while providing effective dialysis and meeting the need for continuous fluid removal in these patients, who often receive a large amount of blood products.\textsuperscript{15}

It is often discussed whether it is appropriate to administer dialysis to critically ill patients with cancer. The data from two studies suggest that the short-term survival rates in critically ill patients with cancer requiring acute dialysis are similar to those of patients without cancer, and renal recovery can be expected in some patients.\textsuperscript{15,26} Less well known is that the onset of AKI in patients with cancer can lead to inadequate or incomplete cancer therapy, thus reducing the potential for cancer cure or longer-term survival. Many patients with cancer are hospitalized electively; this circumstance provides an opportunity to test the efficacy of AKI prevention or preconditioning strategies, especially in those at high risk for AKI, such as patients with diabetes, hematologic cancer, or myeloma, or patients receiving nephrotoxic chemotherapy or allogeneic stem cell transplantation.\textsuperscript{4,13,27}

**Figure 1.** Chemotoxicity and kidney injury. This vicious cycle leads to enhanced systemic toxicity.

**CKD Burden in Cancer**

The striking increase in cancer survivors due to early diagnosis and newer, more effective treatments has also increased the number of survivors with CKD. Chemotherapeutic agents, such as platinum-based compounds, ifosfamide, anti-VEGF agents, tyrosine kinase inhibitors, methotrexate, and several other drugs used for cancer therapy cause AKI, which results in residual CKD.\textsuperscript{3} CKD is also prevalent in patients who have received therapy for renal cell carcinoma (because therapy often involves nephrectomy and anti-VEGF treatment), in patients with myeloma, and in patients with cancer receiving a conditioning regimen and stem cell transplantation.\textsuperscript{11,27,28} Because many cancer survivors have residual renal injury and survival is significantly lower in patients with cancer who have CKD, avoidance of AKI or progression to CKD in cancer survivors has important implications.\textsuperscript{21}

Patients with CKD are also often excluded from hematopoietic stem cell transplantation because of unacceptable morbidity and mortality. In patients with myeloma and ESRD, simultaneous allogeneic stem cell transplantation and kidney transplantation from an HLA-matched donor has been used.\textsuperscript{19} Patients with cancer who have CKD may, thus, benefit from early referral to a nephrologist and long-term nephrology follow-up visits.

**Unique Chemotherapeutic Challenges in CKD and ESRD Populations**

Anticancer therapy can be challenging, especially when the patient’s renal function is compromised. Although most of the anticancer drugs are eliminated through the kidneys, formal data on renal or dialysis clearance for these drugs are scarce and often incomplete. The available dosage recommendations of these agents for the CKD-ESRD population are based on data from small series, case reports, and expert opinion.\textsuperscript{29} Few studies are available to validate the dosing recommendations. A pharmacokinetic modeling study of chemotherapeutic agents used in patients with cancer undergoing dialysis suggested that these agents are generally overdosed.\textsuperscript{30} Overdosing can aggravate systemic toxicities, with fatal consequences, whereas
underdosing can lead to ineffective cancer treatment. Thus, because the CKD-ESRD population has a higher prevalence of cancer and the CKD-ESRD population is increasing, more precise dosing recommendations for this population are needed.31

One suggestion would be for the regulatory agencies, such as the U.S. Food and Drug Administration and the European Medicines Agency, to encourage that essential data on renal and dialysis clearance on new chemotherapeutic agents be made available. Monitoring renal function in patients receiving chemotherapy is essential; however, using serum creatinine in malnourished patients with cancer can overestimate kidney function, thereby risking chemotoxicity. Furthermore, monitoring nephrotoxicity by using serum creatinine will delay the identification of kidney injury, especially in patients with normal baseline function and a large renal reserve. More reliable measures are to use GFR to ensure appropriate dosing based on actual kidney function and kidney injury biomarkers to ensure early detection of kidney injury.22

Fluid-Electrolyte Abnormalities in Cancer

Fluid and electrolytes abnormalities are extremely common in patients with cancer receiving chemotherapy because of the associated nausea, vomiting, and diarrhea and effects of the underlying disease on the nephron. In a recent survey, hyponatremia was noted in nearly 50% of hospitalized patients with cancer.32 Although syndrome of inappropriate antidiuretic hormone due to tumor-associated ectopic antidiuretic hormone, chemotherapeutic agents, nausea, antidepressants, pain, or pain medications is a widely known cause of hyponatremia in patients with cancer, intravenous hydration used during chemotherapy is a frequent cause for worsening hyponatremia. Hyponatremia is associated with an increase in mortality in patients with cancer.32 Therapy for hyponatremia in patients with cancer is similar to that in noncancer settings, although in practice sodium chloride tablets are more frequently used than the imposition of strict fluid restriction. Hypokalemia is also common in patients with cancer, mostly because of reduced potassium intake and excess gastrointestinal loss but occasionally because of endocrine tumors.33 Renal tubular injury can occur from myeloma proteins and several drugs that are tubular toxins causing potassium wasting and hypokalemia.3,34 Steroids used as part of a chemotherapeutic regimen can, through their mineralocorticoid effects, also cause hypokalemia. Unlike in the noncancer setting, hypomagnesemia is fairly common in patients with cancer, especially those receiving some of the above-mentioned tubular toxins. A major adverse effect of cetuximab that targets the epidermal growth factor receptor is the occurrence of reversible urinary magnesium loss leading to hypomagnesemia, a finding that has helped to clarify the role of epidermal growth factor receptor in tubular magnesium transport.35,36 Treating hypomagnesemia in patients with cancer can be challenging and may occasionally require intravenous administration because large doses of oral magnesium can provoke severe diarrhea.37

Hypophosphatemia is more common than hyperphosphatemia in patients with cancer, but both can occur in the setting of several cytotoxic drugs. Uptake of phosphorus by rapidly growing tumors can occasionally cause hypophosphatemia, whereas rapid breakdown of tumors with chemotherapy, exemplified by tumor lysis syndrome associated with Burkitt lymphoma treated with rituximab, can lead to severe hyperphosphatemia. Derangement in calcium homeostasis is fairly common in patients with cancer. Hypercalcemia can be mediated by tumor-secreted parathyroid hormone–related protein or from tumor-induced osteolysis or excess calcitriol production.38 Tumors may also release cytokines that activate osteoclasts directly or through such mediators as granulocyte macrophage colony-stimulating factors.39 Availability of several drugs for treating hypercalcemia, including the potent bisphosphonates, has dramatically improved hypercalcemia management in patients with cancer, but some of these drugs are associated with their own nephrotoxicity.40

### Table 1. Common clinical issues related to nephrologic management in patients with cancer

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<th>Issue</th>
<th>Management</th>
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<td>Sepsis and septic shock</td>
<td>Severe fluid and electrolyte derangements</td>
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<td>Severe acid-base disorders</td>
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<td>Myeloma-related kidney injury</td>
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for research and clinical care; and potentially attract more residents into nephrology for training. Cancer care centers will probably increasingly employ full-time onconephrologists and have nephrology clinics that are integral to their overall care of cancer survivors.

**ONCONEPHROLOGY FORUM: THE OBJECTIVE AND FUNCTION**

A natural question is why there is a need for a separate onconephrology group or organization; couldn’t the general nephrologist take care of patients with cancer? Yes, they can, as we have been doing this. But, as noted earlier, many of the nephrologic issues in patients with cancer are often complex and sometimes unique. Deeper understanding and more experience with these issues are optimal to improve patient outcomes. Additionally, onconephrology also represents an untapped opportunity for expanding nephrology practice, training, and research opportunities, including an increased focus on cancer biology.

Several nephrologists working with patients with cancer believe that nephrologists caring for cancer-related nephrologic problems are indispensable members of the multidisciplinary cancer care team; a multidisciplinary model for cancer care is increasingly adopted by larger cancer centers, such as MDACC in Houston, Memorial Sloan-Kettering Cancer Center in New York, and Dana Farber/Brigham and Women’s Hospital Cancer Center in Boston. These centers have instituted this approach to improve cancer outcomes. Furthermore, several aspects of cancer biology have implications for understanding the pathophysiology and management of renal diseases. Patients with cancer are generally avoided in noncancer kidney research, yet this population can be unique in the context of addressing certain clinically relevant nephrologic research questions. For example, the utility of novel AKI biomarkers can be studied in patients with head and neck cancer who receive cisplatin. Preconditioning strategies to prevent AKI can be applied to electively admitted patients with cancer. The factors leading to the high rates of progression of AKI to CKD in patients with myeloma may lead to better insight into the role of AKI in CKD progression in other settings. The hope is that a focused approach by nephrologists to cancer nephrology, as envisioned by the ONF, will expand the role of appropriately trained nephrologists in the medical management of renal cell carcinoma (an increasing problem in the ESRD population) and multiple myeloma. Such involvement of specially trained medical subspecialists in the primary management of cancer will not be unprecedented. For example, it is routine for specially trained endocrinologists to treat patients with thyroid cancers.

We believe onconephrology is the latest frontier in the war against kidney disease, and it opens up new vistas for the specialty of nephrology to expand its role in patient care and research beyond its conventional realm. Many cancer centers recognize the value of having dedicated nephrologists and are beginning to have their own nephrology section (e.g., Memorial Sloan-Kettering Cancer Center and MDACC) or dedicated onconephrologists to care for their patients (Wayne State University in Detroit; Cleveland Clinic in Cleveland; Dana Farber/Brigham and Women’s Hospital Cancer Center).

One of the authors (A.K.S.), recognizing the importance of onconephrology and the need for onconephrologists to remain in close communication with the larger nephrology community, made initial overtures to several nephrologists working with patients with cancer in the United States in 2009 to determine the feasibility of having an onconephrology-focused organization. As a result, nephrologists working with patients with cancer across the United States had their first meeting, as the ONF, at the 2010 meeting of the American Society of Nephrology in Denver, Colorado. Further discussion between the onconephrologists and Dr. Bonventre, then president of the American Society of Nephrology, led to the organization of the ONF functioning as a focus group. More information can be found at [http://www asn online org/about committees committee aspx? panel OncoNeph](http://www.asn-online.org/about/committees/committee.aspx?panel=OncoNeph).

**CONCLUSION**

Progress in cancer treatments has made renal disease a growing concern in this population. We suggest an increased focus on onconephrology as an identifiable innovative subspecialty of nephrology. We believe this will enhance the competitiveness of nephrology as a medical specialty among trainees and extend the scope of specialty cancer research. With focused research and greater understanding of cancer nephrology, the nephrologic care of patients with cancer can be expected to improve substantially. Several initial steps have been taken: The onconephrologists in the United States have formed the ONF, and the American Society of Nephrology has initiated a 1-day postgraduate onconephrology training course as part of the premeeting program during Kidney Week, including colloquia on onconephrology topics. We hope that these early important steps will ultimately lead to a thriving new role for nephrology at the intersection with oncology.

**DISCLOSURES**

A.K.S. has received an educational grant support from Otsuka Pharmaceutical Co., Ltd. for a proposal to develop onconephrology as special interest area in nephrology. J.V.B. is a co-inventor on KIM-1 patents that are assigned to Partners Healthcare and licensed by Partners to Johnson and Johnson, Sekisui, Biodenldce, and a number of research reagent companies. J.V.B. is a consultant for Sekisui.

**REFERENCES**

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