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Onconephrology: the need and the emergence of a subspecialty in nephrology

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Onconephrology is a new and evolving field of subspecialization in nephrology that deals with the study of kidney diseases in cancer patients, and, by extension, a nephrologist who further specializes in onconephrology can be considered as an onconephrologist. Remarkable advances in cancer medicine have required many cancer programs to become subspecialized, for example, into lymphoma/myeloma, leukemia, stem-cell transplantation (SCT), and various solid-tumor programs. Onconephrology, however, is a broad term that currently encompasses kidney diseases in any cancer setting, whether the tumor is liquid or solid, although further specialization—for example, onconephrology in hematological cancer—remains a possibility.

Much of renal disease in cancer patients is unique (**Table 1**), and they are becoming increasingly complex to manage because of the wider use of conditioning regimens and SCT and the introduction of newer and potentially nephrotoxic cancer therapies. Management of renal disease can be challenging especially in the presence of continued use of nephrotoxic drugs. Tumor lysis syndrome that is unique to cancer can overwhelm the kidneys' ability to excrete the tumor-derived toxic metabolites, often necessitating emergent dialysis. The syndrome of inappropriate antidiuretic hormone secretion, first described in lung cancer patients, is frequent in cancer patients, but their management can be difficult until the cancer is brought under control. Management of kidney injuries associated with SCT and chemotherapy requires specialized understanding of common causes and often requires close interaction with oncologists to achieve the best patient care—timing of dialysis, adjustment of medication doses for prevailing glomerular filtration rate, and so on. Cancer presenting as glomerulonephritis is rare but is almost always seen by nephrologists. However, the primary target for treatment in this setting is cancer. Thrombotic microangiopathy is common in cancer patients and has diverse etiology. Fluid, electrolytes, and acid–base disturbances are much more common in cancer patients and occasionally severe because of myeloma- or drug-induced Fanconi-like tubulopathy. Intractable tubular magnesium wasting is seen in patients receiving epidermal growth factor receptor antagonists. Use of several chemotherapeutic agents, unique and unavoidable in cancer, can be associated with acute and chronic kidney injuries. Newer targeted cancer therapies such as anti-vascular endothelial growth factor (anti-VEGF) and tyrosine kinase inhibitors are also associated with similar kidney injuries, as well as proteinuria, hypertension, and thrombotic microangiopathy. With the emergence of a new era of cancer immunotherapy especially with the use of antibodies, cytokines, vaccines, and cellular therapies, the renal injuries due to patients' inflammatory responses can be profound. For example, the use of interleukin-2 therapy in advanced renal-cell carcinoma (RCC) or melanoma can lead to renal failure, often to the brink of needing dialysis. However, discontinuation of therapy and effective volume management often readily reverses the renal failure, avoiding dialysis.

There are also several unaddressed research and clinical questions in onconephrology, and identifying onconephrology as a subspecialized field can help advance much-needed new research and guidelines in managing kidney disease in cancer patients. Some research areas are: (1) proactive approaches to prevent or minimize acute kidney injury (AKI) in cancer patients; (2) study of BK nephropathy in the SCT population, including new therapeutic trials; (3) further characterization of kidney disease of veno-occlusive disease and testing of therapeutic strategies to mitigate it; (4) evaluation of the significance of proteinuria and renal dysfunction as a unique presentation of graft-versus-host disease in SCT patients; (5) creation of a national renal toxicity database for older and newer chemotherapeutic

Table 1 | Kidney diseases in common cancers

Leukemia
Common: AKI from sepsis, volume depletion, drug toxicity
Rare: Infiltrative disease, glomerulonephritis, AKI from TLS
Myeloma
Common: Myeloma kidney, AKI from volume depletion
Rare: Amyloidosis, LCDD, Fanconi's syndrome, AKI from hypercalcemia
Lymphoma
Common: AKI from TLS and volume depletion
Rare: Obstructive uropathy, infiltrative disease, minimal-change disease (Hodgkin's), MPGN (non-Hodgkin's lymphoma)
Renal-cell carcinoma
Common: Anti-VEGF toxicity after nephrectomy
Rare: Obstructive uropathy, membranous nephropathy
Lung and head and neck cancer
Common: Platinum toxicity
Rare: SIADH, membranous glomerulonephritis
Genitourinary and gynecological cancers
Common: Obstructive uropathy
Rare: Platinum toxicity
Kidney disease in commonly used cancer treatments
Common: AKI, tubulopathy, and CKD from chemotherapeutic agents, e.g., cisplatin, ifosfamide, and methotrexate, complications of conditioning regimen, and HSCT, and from toxicities of targeted anticancer therapies (includes proteinuria, TMA, and hypertension)
Rare: Radiation nephritis, TMA, glomerulonephritis

Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; HSCT, hematopoietic stem-cell transplantation; LCDD, light chain deposition disease; MPGN, membranoproliferative glomerulonephritis; SIADH, syndrome of inappropriate antidiuretic hormone secretion; TLS, tumor lysis syndrome; TMA, thrombotic microangiopathy; VEGF, vascular endothelial growth factor.

agents; (6) use of pharmacokinetic data for dosing recommendations for chemotherapeutic agents in the chronic kidney disease (CKD) and end-stage renal disease (ESRD) populations and for the timing of dialysis; and (7) ongoing evaluation of kidney diseases related to myeloma and amyloid in the context of evolving oncological treatment—to mention a few areas. A brief Internet search revealed very little research funded by the US National Institutes of Health (NIH) or the National Cancer Institute in topics related to cancer nephrology. Under the Foundation for the NIH, a large multicenter study on AKI biomarkers in patients receiving potentially nephrotoxic drugs, including cisplatin in cancer patients, is currently under way. Clinical studies testing, for example, preconditioning strategies in hospitalized cancer patients who are at high risk for AKI are warranted. With the profusion of new cancer drugs, renal side effects have to be closely monitored and reported. Opportunities for nephrology research in cancer patients are plenty, and hopefully the onconephrology community will pursue such goals.

In the past three years, several original articles related to onconephrology have appeared in nephrology and cancer journals, a number of books on cancer nephrology have appeared or are in preparation, and onconephrology chapters are appearing in major nephrology textbooks. A Google search on 6 August 2013 for 'onconephrology' yielded 1940 hits, and a search for 'onconephrology,' 'onco-nephrology,' or 'onco nephrology' in PubMed yielded a total of 26 articles. In addition, the *Nephrology Self-Assessment Program* published an issue on "Cancer and the Kidney" in 2013, further illustrating the different renal diseases and challenges in managing cancer patients. The *Clinical Journal of the American Society of Nephrology* published a series on onconephrology in 2012.[1] Moreover, there are many nephrologists working on myeloma research, amyloidosis, SCT, chemotoxicities, and dosing of chemotherapy agents in CKD and ESRD, and even nephropathologists working on such topics as thrombotic microangiopathy from SCT. Recognizing the uniqueness of cancer nephrology and the need for a forum at the national level, a number of nephrologists working in the main cancer centers of the United States formed the OncoNephrology Forum under the American Society of Nephrology in 2011.[2]

Endocrinologists have traditionally treated most endocrine tumors. With the probable emergence of onconephrology as a subspecialty, a formalized one-year onconephrology fellowship training program after the traditional nephrology fellowship (possibly 6 months of clinical and 6 months of research in cancer nephrology in a nephrology fellowship program affiliated with a Comprehensive Cancer Center) would help transform onconephrology into a distinct discipline within nephrology, similar to transplant nephrology. This would enhance the choices within the specialty of nephrology. The onconephrology fellowship training could include training for managing RCC under medical genitourinary oncology. A trained onconephrologist in this role is well suited to medically treat RCC, as he or she can deal better with the renal side effects of hypertension, proteinuria, and renal failure of current therapies for RCC such as anti-VEGF drugs, and with the CKD and ESRD that may follow nephrectomies, a common treatment for RCC. Moreover, RCC is reported to be more frequent in the CKD–ESRD population.[3]

In summary, unique and unprecedented opportunity exists for nephrology to move into the specialized care of nephrological problems in cancer patients. These onconephrological opportunities, with additional opportunity for teaching and training medical residents and nephrology fellows and undertaking nephrology-relevant research, are available worldwide, and promoting onconephrology at the international level fits nicely with the stated goals of the International Society of Nephrology.

DISCLOSURE

The authors declared no competing interests.

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