ONCO-NEPHROLOGY: A DECALOGUE

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Onco-Nephrology is a new and evolving subspecialty that focuses on all aspects of kidney disease in cancer patients (1). As the name implies, nephrologists and oncologists are well positioned to collaborate on this rapidly growing and increasingly complicated area of medicine. Although a number of Editorials and Letters highlighting many of the potentials of this novel discipline have been recently published in both Oncology and Nephrology journals (1-3), they only represent the tip of the iceberg and likely underestimate the actual depth of collaboration that is possible for the two specialties. In this regard, based on the current and expanding interaction that exists between cancer and the kidneys, it is important for those involved in the field to describe the areas of interest in Onco-Nephrology that, in our opinion, have not been clearly and completely established. Our Colleagues may have understated the degree of interest and all of the potential areas of contact (and thus are of reciprocal interest) that exist between the two specialties (Table 1). In this opinion piece, we propose a "decalogue of Onco-Nephrology", in order to highlight the areas where the Nephrologist and Oncologist should work closely over the ensuing years to provide cutting edge care for patients afflicted with cancer and kidney disease.

1) Acute kidney injury (AKI) and chronic kidney disease (CKD) in cancer patients

The presence of AKI or CKD in a cancer patient has a negative impact on many aspects of patient care. The presence of kidney impairment quite often affects his/her cancer treatment and overall prognosis. Indeed, oncologic patients have an increased risk of developing AKI within the first year from the diagnosis of cancer, and this combination negatively affects their survival (4). This is particularly true for the eldery, who have the highest cancer incidence rates (5) and 10-fold higher AKI rates compared with the non-elderly population (6). As seen with AKI, the IRMA study clearly demonstrates that CKD is also quite prevalent in cancer patients (7). Most concerning is the increased mortality noted in cancer patients with AKI/CKD as compared with those without kidney disease. Furthermore, the relationship between kidney disease and cancer is 'circular'. Indeed, pre-existing CKD in some instances may disturb the bioavailability and/or safety profile of certain oncological drugs, potentially leading to suboptimal treatments, or enhance risk for drug-induced de novo kidney injury or worsening of a CKD. Finally, some very effective anticancer agents may be avoided as a potential option in CKD patients due to the lack of specific information on their pharmacokinetic properties in this setting. The growing prevalence of cancer and AKI/CKD implies that an increasing number of patients will require the expertise of an Onco-Nephrologist, who

must be knowledgeable about the vast array of anticancer agents, their pharmacokinetics in patients with CKD, and their potential toxic effects on kidney function.

2) Nephrotoxic effects of anticancer therapy

A number of anticancer agents may directly or indirectly affect the kidneys. While the nephrotoxicity associated with traditional cytotoxic agents (e.g. Cisplatin) is well characterized (8), the recent development of a large number of molecularly targeted agents and their release into clinical practice has dramatically widened the spectrum of adverse renal events. Indeed, like opening Pandora's box (9), a wide array of previously unrecognized and ill-defined abnormalities of kidney function, such as hypertension, proteinuria, acute interstitial nephritis (AIN), thrombotic microangiopathy, and various electrolyte/acid base disorders are are increasingly being observed with these targeted agents (10). This once again highlights the need for a specially trained clinician with specific knowledge of these complications to be available for patients that receive these drugs.

3) ***Paraneoplastic renal manifestations***

Various forms of paraneoplastic kidney injury occur as a result of non-direct, distant toxicities of malignancy that are unrelated to drug-induced nephrotoxicity. These rare events, which include paraneoplastic glomerulonephritis (membranous, minimal change, focal segmental glomerulosclerosis, membranoproliferative, etc), electrolyte/acid-base disturbances, thrombotic microangiopathies, or glomerular diseases associated with hematopoietic stem cell transplantation (whose incidence appears to be increasing), often represent a complex differential diagnosis and often pose a difficult issue for clinicians (11). Thus, both the Nephrologist and Oncologist need to be aware of the occurrence of cancers with these syndromes, of their clinical characteristics, and on how to effectively manage them. Furthermore, clinicians must decide on the appropriate approach to certain types of paraneoplastic syndromes. For example, in a patient who develops a putative 'paraneoplastic glomerulopathy', should we commence screening for the possibility of an occult cancer? If the consensus is affirmative, we must then decide how to 'screen' patients and how often we must repeat the process to avoid missing the malignancy at an eraly stage. Collaboration between the Nephrologist and Oncologist is thus critical again.

4) Kidney cancer nephrectomy management

Kidney cancer remains the only malignancy where either total or partial nephrectomy is indicated (12). This includes not only localized, curable tumors, but also incurable, metastatic malignant disease (12). It has been clearly demonstrated that patients who have undergone nephrectomy are at increased risk of developing AKI, de novo CKD, especially in the presence of certain co-morbidities, or of worsening a pre-existent CKD, which is highly prevalent in these patients prior to nephrectomy (13). In addition, partial nephrectomy, which is considered nephron-sparing, may also cause AKI or worsen underlying CKD, depending on the amount of non-neoplastic parenchyma removed (13). Knowledge of those risk factors that promote acute or chronic kidney injury following these procedures are in the perview of the Onco-Nephrologist and must be considered with the Urologist prior to nephrectomy. Furthermore, metastatic disease poses a higher risk for developing adverse renal events such as hypertension and/or proteinuria as well as non-renal toxicities (e.g. hand-foot syndrome or fatigue) with exposure to targeted anti-cancer agents (9,10). Thus, while the Urologist is primarily involved, close follow-up by both the Nephrologist and Oncologist is warranted for all nephrectomized patients.

5) Renal replacement therapy and active oncological treatments

One of the more challenging areas of Onco-Nephrology is the appropriate management of cancer patients that require renal replacement therapy (RRT) for either AKI or end-stage renal disease (ESRD). Decisions about anti-cancer drug choice and dosing is often not supported by pharmacokinetic or pharmacodynamic data, making therapeutic decisions difficult (10). Where data are available, the Nephrologist should be well versed on the effects of the various dialytic modalities on drug clearance. Basic understanding of the effects of CRRT/hemodialysis/peritoneal dialysis on general drug clearance (volume of distribution, protein binding, molecular size, etc) will allow reasonable estimates on the safety of anti-cancer drug dosing in such patients. Knowledge of anti-cancer drug interactions with other prescribed medications is also critical. Furthermore, the decision to initiate RRT or not in a cancer patient with ESRD remains a major ethical issue (14), which is best resolved by taking into account prognosis (in terms of life expectancy), quality of life, and the patient's and his/her families wishes. It is these particular issues, patient cancer prognosis and quality of life, that once again highlight the importance of the collaboration between the Oncologist and Nephrologist.

6) Cancer survivors and kidney transplantation

Another setting that requires a close working relationship between the Nephrologist and Oncologist is in the evaluation of an ESRD patient with a previously treated maligancy for kidney transplantation. The question posed "How long to wait before placing such an ESRD patient on the transplantation list?" can be difficult. What is a sufficient time to consider a patients cured and able to receive a graft and undergo immunosuppression therapy? Even more complex is dealing the flip side of this issue—is the patient with a previously treated malignancy a suitable kidney donor? In such a scenario, are all malignancies considered the same in this regard? Potential complications exist for both the donor and recipient. Furthermore, if the patient is considered a suitable candidate, how much time should have elapsed from the original cancer diagnosis? Presently, all of these questions have no clearcut or evidence-based answers. Obviously, while such data are sorely needed, expert opinion and experience from the Onco-Nephrology collaboration is the next best option. Along the same lines, ESRD patients on the transplant waiting list have a higher incidence and prevalence of cancer compared with the general population (15) and therefore require cancer monitoring to avoid transplantation in the setting of malignancy.

7) Oncological treatment in kidney transplant patients

Cancer is observed with increasing frequency in kidney transplant recipients receiving long-term immune suppression (16). Management can be difficult and complicated by balancing treatment of the malignancy with maintenance of a functioning kidney. Saving the kidney is not always possible, but may be attempted depending on the cancer status and patient's wishes. The development of metastatic cancer in such a patient raises the issue of choosing the most appropriate immunosuppressive regimen, or said another way, not choosing the worst (and most potent immunosuppressing) regimen in the setting of cancer. One useful approach to be considered in this setting is employment of an mTOR inhibitor. Given their anticancer effects observed in registry-based retrospective data (17), which are observed at completely different doses, it is a reasonable consideration that the treating team can contemplate. An ideal answer to this therapeutic dillema is a prospective, randomized trial, although the trial design and conduct would be fraught with difficulty.

8) Pain management in patients with cancer and kidney disease

Without a doubt, pain is probably the worst experience a cancer patient must endure. Despite the availability of a number of highly active analgesic drugs, use of certain drugs can be problematic in cancer patients with either acute or chronic kidney disease. For example, some medications like the NSAIDs have the potential to worsen kidney function and/or induce electrolyte/acid-base disturbances in patients with underlying AKI or pre-existing CKD (18,19). Other analgesics such as opioids may not adversely affect kidney function but may accumulate in the setting of AKI, CKD or ESRD, leading to potentially harmful complications (20). As use of these medications can be a double-edged sword (21), pain management should be cautiously directed by those familiar with drug pharmacology in cancer patients with kidney disease .

9) Development of integrated guidelines Onco-Nephrology patients

The new area of Onco-Nephrology suffers from a lack of guidance for clinicians who encounter difficult and often complex problems in this complicated group of patients. As kidney disease is common in cancer patients, and growing data suggests that cancer is also prevalent in CKD and ESRD patients, clinicians will commonly encounter these groups. It also appears that the relationship between cancer therapy and kidney disease is under-explored, with very little data available. This deficiency has multiple explanations and include: A) selection bias of randomized controlled phase III trials, where patients are enrolled only if they have a conserved kidney function; B) difficulty in interpreting the nature and incidence of renal adverse events from these trials; C) lack of uniformity in the definition of kidney impairment between oncological trials, summary of product characteristics, and nephrologic classification; and D) availability of only case reports or small case series for patients undergoing dialysis (10). Thus, experience-based guidelines in the interpretation and employment of anti-cancer therapy would be beneficial. In addition, guidelines that provide insight into the diagnosis and management of several issues encountered in specific areas of Onco-Nephrology would help clinicians. Some specific situations include: 1. follow-up of the cancer patient with CKD; 2. prevention and management of contrast-induced nephropathy (22); 3. diagnosis and management of electrolyte and acid-base disturbances (e.g. hypo/hyperkalemia, hypo/hypercalcemia, hypomagnesemia, hypo/hyperphsophatemia, lactic acidosis, etc); 4. pre and post-nephrectomy management for renal cancer; 4. management of anemia (23) in the cancer patient with CKD receiving or not active oncologic treatments; and management of the renal transplantation patient with cancer.

10) Clinical trial design specific to Onco-Nephrology

As we move the field of Onco-Nephrology forward, it is imperative that our group begins to design and conduct randomized, controlled clinical trials (and other trial design) aimed at addressing many of the issues and questions raised in this paper. Only then can we provide evidence-based care to this complicated group and ultimately improve their outcomes.

Thanks to the dramatic improvements in cancer treatment and care, a number of men and women afflicted by cancer can now survive longer, sometimes with a near normal life-expectancy. However; longer survival with an assortment of chronic diseases, including both acute and chronic declines in kidney function, complicate their care. In addition to the adverse effects of the tumor itself, knowledgeable healthcare providers will need to carefully manage ongoing tumor therapy (in the setting of kidney disease) and acute and/or chronic kidney disease and their assorted complications. A multi-disciplinary Onco-Nephrology team, led by the Oncologist and Nephrologist, will be critical to provide outstanding, cutting edge care in both the acute and chronic setting to this group of cancer patients. In this decalogue, we believe that the development of a subspecialty in Onco-Nephrology is required to achieve these goals. This is just a start and large amount of work lies ahead for us. Only by working together will the Nephrologist and Oncologist succeed in this endeavor.

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Table 1 – Patients and issues in Onco-Nephrology.

• Cancer patients with underlying kidney disease or risk factors for kidney injury	1. Very few data available from randomized, controlled, trials 2. Toxic renal effects of anticancer therapy (either traditional chemotherapeutics or molecularly targeted agents) 3. Toxic renal effects of other drugs (e.g. bisphosphonates, anti-pain drugs, etc) 4. Toxic renal effects of other anticancer treatments (e.g. radiotherapy) 5. Risk of undertreatment for cancer patients with AKI or CKD
• Cancer patients on hemodialysis	1. No data available from randomized, controlled, trials 2. Unknown or poorly described pharmacokinetic properties of anticancer therapy (either traditional chemotherapeutics or molecularly targeted agents) in this setting 3. Unknown timing and dose of administration of anticancer therapy with respect of dialysis 4. Nihilistic approach to cancer patients on dialysis
• Transplanted patients or those on the waiting list	1. Immune suppressive therapy and risk of developing cancer 2. If and when to put a cancer survivor into transplantation list for ESRD 3. How to deal with organs from donors with previous or active tumors 4. Ideal immunosuppression in the case of development of cancer following transplantation
• Patients with kidney cancer and/or those undergoing nephrectomy	1. Best surgical procedure to achieve the best oncological as well nephrological outcome 2. Higher risk of developing toxicities from molecular targeted agents in metastatic patients 3. Pre-surgery eGFR associated with an higher risk of developing post-operative AKI or worsening of pre-existent CKD
• All cancer patients	1. Need of integrated guidelines for the cancer patient with kidney disease 2. Need of clinical trials addressing specific onco-nephrological issues