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# Onco-nephrology: a decalogue

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## ABSTRACT

Onco-nephrology is an evolving subspecialty that focuses on the complex relationships existing between kidney and cancer. 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. The 10 points we have highlighted include (1) acute kidney injury and chronic kidney disease in cancer patients; (2) nephrotoxic effects of anticancer therapy, either traditional chemotherapeutics or novel molecularly targeted agents; (3) paraneoplastic renal manifestations; (4) management of patients nephrectomized for a kidney cancer; (5) renal replacement therapy and active oncological treatments; (6) kidney transplantation in cancer survivors and cancer risk in ESRD patients; (7) oncological treatment in kidney transplant patients; (8) pain management in patients with cancer and kidney disease, (9) development of integrated guidelines for onco-nephrology patients and (10) clinical trials designed specifically for onco-nephrology. Following these points, a multidisciplinary onco-nephrology team will be key to providing outstanding, cutting-edge care in both the acute and chronic setting to these patients.

**Keywords:** AKI, cancer, CKD, dialysis, nephrectomy, nephrotoxicity

## INTRODUCTION

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 represent only 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 (which are thus 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.

### Acute kidney injury and chronic kidney disease in cancer patients

The presence of acute kidney injury (AKI) or chronic kidney disease (CKD) in cancer patients has a negative impact on many aspects of patient care. The presence of kidney impairment quite often affects a patient's 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 elderly, who have the highest cancer incidence rates [5] and 10-fold higher AKI rates

**Table 1. Patients and issues in onco-nephrology**

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



compared with the non-elderly population [6]. As seen with AKI, the Renal Insufficiency and Cancer Medications (IRMA) study clearly demonstrates that CKD is also quite prevalent in cancer patients [7] and that the survival rate at 2 years was significantly lower for patients with concomitant CKD [8]. 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 sub-optimal treatments, or enhance risk for drug-induced *de novo* kidney injury or worsening of CKD [9]. 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.

As a consequence, therapeutic drug monitoring in cancer patients with CKD, especially in an advanced stage or in the case of an overt end-stage renal disease (ESRD), is of the utmost importance if and when an active oncological treatment is started.

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 [10]; thus, a close collaboration with pharmacologists/hospital pharmacists is warranted to check, report and, whenever possible, prevent drug-induced adverse events.

## 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 [11], 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 [12], a wide array of previously unrecognized and ill-defined abnormalities of kidney function, such as hypertension, proteinuria, acute interstitial nephritis, thrombotic microangiopathy and various electrolyte/acid–base disorders, are increasingly being observed with these targeted agents [13]. This once again highlights the need for specially trained clinicians with specific knowledge of these complications who can treat patients receiving these drugs.

## 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 [14]. Thus both the nephrologist and oncologist need to be aware of the occurrence of cancers with these syndromes, their clinical characteristics and how to effectively manage them. Furthermore, clinicians must decide on the appropriate approach to treat 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 early stage. Once again, it becomes apparent that the collaboration between the nephrologist and oncologist is critical.

### Management of patients nephrectomized for a kidney cancer

Kidney cancer remains the only malignancy where either total or partial nephrectomy is indicated [15]. This includes not only localized, curable tumours, but also incurable, metastatic malignant disease [15]. 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 [16]. 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 [16]. Knowledge of those risk factors that promote acute or chronic kidney injury following these procedures is within the purview 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 anticancer agents [12, 13]. Thus, while the urologist is primarily involved, close follow-up by both the nephrologist and oncologist is warranted for all nephrectomized patients.

### 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 ESRD, a patient population characterized by low survival rates [17]. Decisions about anticancer drug choices and dosing are often not supported by pharmacokinetic or pharmacodynamic data, making therapeutic decisions difficult [13]. Where data are available, the nephrologist should be well versed on the effects of the various dialytic modalities on drug clearance. A basic understanding of the effects of continuous RRT/haemodialysis/peritoneal dialysis on general drug clearance (volume of distribution, protein binding, molecular size, etc.) will allow reasonable estimates of the safety of anticancer drug dosing in such patients. Knowledge of anticancer 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 [18], which is best resolved by taking into account prognosis (in terms of life expectancy), quality of life and the wishes of the patient and his/her family. 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.

### Kidney transplantation in cancer survivors and cancer risk in ESRD patients

Another setting that requires a close working relationship between the nephrologist and oncologist is in the evaluation for transplantation of an ESRD patient with a previously treated malignancy. The question of how long to wait before placing such an ESRD patient on the transplantation list can be difficult. What is a sufficient length of time to consider a patient as cured and able to receive a graft and undergo immunosuppression therapy? Even more complex is dealing with 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 clear-cut 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 [19] and therefore require cancer monitoring to avoid transplantation in the setting of malignancy. However, beyond pure epidemiological considerations, cancer screening in patients with CKD/ESRD has a cost that should be weighed against its benefits in a global situation characterized by a dramatic shortage of resources. At present, cancer screening seems not to be cost effective in the setting of ESRD. Indeed, an old prospective study [20] showed that the costs per unit of survival benefit conferred by cancer screening were 1.6 to 19.3 times greater among patients with ESRD than in the general population, depending on age, sex and race. Furthermore, for patients with ESRD, the net gain in life expectancy from a typical cancer-screening program was calculated to be $\leq$5 days, and similar survival gains could be obtained via a reduction of $\leq$0.02% in the baseline ESRD-related mortality rate [20]. The authors thus concluded that routine cancer screening in the population of ESRD patients is a relatively inefficient allocation of financial resources and that direction of funds towards improving the quality of dialysis could attain such an objective at substantially lower cost [20]. However, it is clear that this study should no longer be considered, having been published almost 20 years ago, within a completely different economic (and medical) scenario.

### Oncological treatment in kidney transplant patients

Cancer is observed with increasing frequency in kidney transplant recipients receiving long-term immuno suppression [21]. 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 a mammalian target of rapamycin inhibitor. Given their anticancer effects observed in registry-based retrospective data [22], which are observed at completely different doses, this is a reasonable consideration that the treating team

may contemplate. An ideal answer to this therapeutic dilemma is a prospective, randomized trial, although the trial design and conduct would be fraught with difficulty.

### 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, the use of certain drugs can be problematic in cancer patients with either acute or chronic kidney disease. For example, some medications such as non-steroidal anti-inflammatory drugs have the potential to worsen kidney function and/or induce electrolyte/acid–base disturbances in patients with underlying AKI or pre-existing CKD [23, 24]. 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 [25]. As the use of these medications can be a double-edged sword [26], pain management should be cautiously directed by those familiar with drug pharmacology in cancer patients with kidney disease.

### Development of integrated guidelines for 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 suggest 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 underexplored, with very little data available. This deficiency has multiple explanations and includes (i) selection bias of randomized controlled phase III trials, where patients are enrolled only if they have a conserved kidney function; (ii) difficulty in interpreting the nature and incidence of renal adverse events from these trials; (iii) lack of uniformity in the definition of kidney impairment between oncological trials, summary of product characteristics and nephrologic classification and (iv) availability of only case reports or small case series for patients undergoing dialysis [13]. Thus, experience-based guidelines in the interpretation and employment of anticancer therapy would be beneficial. A first valuable step has been performed by the European Medicines Agency, which, in 2014, published updated guidelines on the evaluation of the pharmacokinetics of medicinal products in patients with decreased renal function (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/02/WC500162133.pdf), to be used by pharmaceutical companies in the development of clinical trials. In addition, other 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 follow-up of the cancer patient with CKD, prevention and management of contrast-induced nephropathy [27], diagnosis and management of electrolyte and acid–base disturbances (e.g. hypo/hyperkalaemia, hypo/hypercalcaemia, hypomagnesaemia, hypo/hyperphsophataemia, lactic acidosis, etc.), pre- and post-nephrectomy management for renal cancer, management of anaemia [28] in cancer patients with CKD, whether or not they are receiving active oncologic treatments and management of the renal transplantation patient with cancer.

Along this line, the Cancer and the Kidney International Network (C-KIN) have recently held its first congress and just published recommendations and guidelines [29].

### 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 here. Only then can we provide evidence-based care to this complicated group and ultimately improve their outcomes.

## DISCUSSION

Thanks to the dramatic improvements in cancer treatment and care, many patients afflicted with 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, complicates their care. In addition to the adverse effects of the tumour itself, knowledgeable healthcare providers will need to carefully manage ongoing tumour therapy (in the setting of kidney disease) and acute and/or CKD and their assorted complications. A multidisciplinary onco-nephrology team, led by an oncologist and nephrologist, but including also other health professionals (e.g. pharmacologists and pharmacists), will be critical to providing 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 the beginning, as a much work lies ahead. Only by working together will the nephrologist and oncologist succeed in this endeavour.

## CONFLICT OF INTEREST STATEMENT

None declared.

## REFERENCES


1. Salahudeen AK, Bonventre JV. Onconephrology: the latest frontier in the war against kidney disease. J Am Soc Nephrol 2013; 24: 26–30
2. Abudayyeh AA, Lahoti A, Salahudeen AK. Onconephrology: the need and the emergence of a subspecialty in nephrology. Kidney Int 2014; 85: 1002–1004
3. Finkel KW, Howard SC. Onco-nephrology: an invitation to new field. J Clin Oncol 2014; 32: 2389–2390
4. Christiansen CF, Johanson MB, Langeberg WJ *et al.* Incidence of acute kidney injury in cancer patients: a Danish population-based cohort study. Eur J Intern Med 2011; 22: 399–406
5. Howlader N, Noone AM, Krapcho M *et al.* (eds). SEER Cancer Statistics Review, 1975–2012, National Cancer Institute. Bethesda, MD. http://seer.cancer.gov/csr/1975_2012/ (22 August 2015, date last accessed)

6. United States Renal Data System. Atlas of CKD. Chapter 6: Acute Kidney Injury. http://www.usrds.org/2012/pdf/v1_ch6_12.pdf (22 August 2015, date last accessed)
7. Launay-Vacher V, Oudard S, Janus N *et al.* Prevalence of renal insufficiency in cancer patients and implications for anticancer drug management: the renal insufficiency and anticancer medications (IRMA) study. Cancer 2007; 110: 1376–1384
8. Launay-Vacher V. Epidemiology of chronic kidney disease in cancer patients: lessons from the IRMA study group. Semin Nephrol 2010; 30: 548–556
9. Verbeeck RK, Musuamba FT. Pharmacokinetics and dosage adjustment in patients with renal dysfunction. Eur J Clin Pharmacol 2009; 65: 757–773
10. Janus N, Thariat J, Boulanger H *et al.* Proposal for dosage adjustment and timing of chemotherapy in hemodialyzed patients. Ann Oncol 2010; 21: 1395–1403
11. Miller RP, Tadagavadi RK, Ramesh G *et al.* Mechanisms of cisplatin nephrotoxicity. Toxins (Basel) 2010; 2: 2490–2518
12. Porta C, Paglino C, Imarisio I *et al.* Uncovering Pandora's vase: the growing problem of new toxicities from novel anticancer agents. The case of sorafenib and sunitinib. Clin Exp Med 2007; 7: 127–134
13. Porta C, Cosmai L, Gallieni M *et al.* Renal effects of targeted anticancer agents. Nat Rev Nephrol 2015; 11: 354–370
14. Bacchetta J, Juillard L, Cochat P *et al.* Paraneoplastic glomerular diseases and malignancies. Crit Rev Oncol Hematol 2009; 70: 39–58
15. Heng DY, Wells JC, Rini BI *et al.* Cytoreductive nephrectomy in patients with synchronous metastases from renal cell carcinoma: results from the International Metastatic Renal Cell Carcinoma Database Consortium. Eur Urol 2014; 66: 704–710
16. Kotamarti S, Rothberg MB, Danzig MR *et al.* Increasing volume of non-neoplastic parenchyma in partial nephrectomy specimens is associated with chronic kidney disease upstaging. Clin Genitourin Cancer 2015; 13: 239–243
17. Janus N, Launay-Vacher V, Thyss A *et al.* Management of anticancer treatment in patients under chronic dialysis: results of the multicentric CANDY (CANcer and DialYsis) study. Ann Oncol 2013; 24: 501–507
18. Berman N. End-of-life matters in chronic renal failure. Curr Opin Support Palliat Care 2014; 8: 371–377
19. Mosconi G, Centofanti F, Capelli I *et al.* Incidence and prevalence of cancer in kidney transplantation waiting list patients: an Italian experience. Int J Artif Organs 2013; 36: 335
20. Chertow GM, Paltiel AD, Owen WF, Jr *et al.* Cost-effectiveness of cancer screening in end-stage renal disease. Arch Intern Med 1996; 156: 1345–1350
21. Navarro MD, Lopez-Andreu M, Rodriguez-Benot A *et al.* Cancer incidence and survival in kidney transplant patients. Transplant Proc 2008; 40: 2936–2940
22. Yanik EL, Gustafson SK, Kasiske BL *et al.* Sirolimus use and cancer incidence among US kidney transplant recipients. Am J Transplant 2015; 15: 129–136
23. Whelton A. Nephrotoxicity of nonsteroidal anti-inflammatory drugs: physiologic foundations and clinical implications. Am J Med 1999; 106: 13S–24S
24. Epstein M. Non-steroidal anti-inflammatory drugs and the continuum of renal dysfunction. J Hypertens Suppl 2002; 20: S17–S23
25. King S, Forbes K, Hanks GW *et al.* A systematic review of the use of opioid medication for those with moderate to severe cancer pain and renal impairment: a European Palliative Care Research Collaborative opioid guidelines project. Palliat Med 2011; 25: 525–552
26. Argoff C. NSAIDs or opioids, damned if you do, damned if you don't?: evidence-based selections to optimize therapeutic goals and minimize harms. Pain Med 2013; 14(Suppl 1): S40–S42
27. Andreucci M, Faga T, Pisani A *et al.* Prevention of contrast-induced nephropathy through a knowledge of its pathogenesis and risk factors. Scientific World J 2014; 2014: 823169
28. Hazzan AD, Shah HH, Hong S *et al.* Treatment with erythropoiesis-stimulating agents in chronic kidney disease patients with cancer. Kidney Int 2014; 86: 34–39
29. Launay-Vacher V, Aapro M, De Castro G, Jr *et al.* Renal effects of molecular targeted therapies in oncology: a review by the Cancer and the Kidney International Network (C-KIN). Ann Oncol 2015; 26: 1677–1684

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