Summary of the International Conference on Onco-Nephrology: an emerging field in medicine

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Abstract

Onco-nephrology is an emerging field in medicine. Patients with cancer may suffer from kidney diseases because of the cancer itself and cancer-related therapy. It is critical for nephrologists to be knowledgeable of cancer biology and therapy in order to be fully integrated in the multidisciplinary team and optimally manage patients with cancer and kidney diseases. In a recent international meeting, the key issues in this challenging clinical interface were addressed, including many unresolved basic science questions, such as the high tumor incidence in kidney transplant recipients. To this end, 70 highly qualified faculty members were gathered from all over the world to discuss these issues in 8 plenary sessions, including 5 keynote lectures. In addition, 48 young nephrologists and oncologists were invited to present their original observations that were highlighted in 2 large poster sessions.

Keywords: acute kidney injury, cancer chemotherapy, chronic kidney disease, nephrotoxicity, renal cell carcinoma.

Introduction

Cancer and kidney disease are both associated with significant morbidity and mortality.1 Over the past decade, nephrologists, oncologists, and other clinicians recognized kidney disease and electrolyte/acid-base disturbances as complications of a malignant tumor. Moreover, chronic kidney disease (CKD) is associated with an increased cancer risk, making the relationship bidirectional. The importance of this cancer–kidney disease connection has prompted the creation of the subfield “onco-nephrology” (Figure 1).2

Both acute kidney injury (AKI) and CKD are prevalent in patients with cancer.3, 4, 5 Incidence and severity of AKI varies depending on type/stage of cancer, treatment regimen, and underlying comorbidities.4, 5, 6 Patients with incident cancer have 1- and 5-year AKI risk of 17.5% and 27%, respectively.7 Critically ill patients with cancer are at an even higher risk, with ∼13% to 54% of patients developing AKI and 8% to 60% requiring dialysis.8, 9 As observed in the Renal Insufficiency and Cancer Medications (IRMA) Study 1 and 2, patients with cancer had a stage 3 CKD prevalence of ∼12%.10, 11 In other cancer cohorts, stage 3 CKD was observed in ∼13% to 30% of patients.12, 13

Major risks of AKI include cancer-related metabolic disturbances, tissue deposition of paraproteins, treatment with nephrotoxic anticancer drugs, and hematopoietic stem cell transplantation.14 Total and partial nephrectomy for kidney cancer also increases the risk of acute kidney disease/CKD.15

Morbidity/mortality is higher in patients with cancer and kidney diseases,6, 10 with the highest mortality in patients with dialysis-requiring AKI.4 Some patients with cancer and CKD may also have an increased risk of death.12, 13, 16 Mortality risk is highest for hematologic malignancies, gynecologic cancers, and renal carcinomas in the setting of CKD.12, 13

Kidney disease increases the risk of systemic chemotherapy toxicity, jeopardizes continued cancer therapy, and limits patient participation in clinical trials. Temporary or permanent cessation of effective chemotherapeutic regimens allows unhindered tumor growth, whereas underdosing of potentially curative regimens or use of suboptimal alternatives reduces treatment efficacy.2, 5 Altered drug pharmacokinetics risk systemic toxicity, whereas uremia impairs immune surveillance, allowing cancers to grow/metastasize. It is also possible that anticancer drug nephrotoxicity leads to progression of AKI and/or CKD, contributing to all-cause mortality unrelated to cancer.

It is critical that clinicians and researchers from multiple specialties develop familiarity with onco-nephrology as the number of patients surviving cancer and kidney disease increases. To this end, the meeting was designed. The summary of the plenary sessions is reported below.

The full conference program and the video recordings of all presentations and discussions can be found at the following website: https://www.en.fondazione-menarini.it/Home/News/Onco-Nephrology-an-Emerging-Field-in-Medicine/Presentation.

Advanced technologies

Researchers worldwide base their experiments using cancer cells in vitro, but to acquire a comprehensive understanding of the complexity of cancer biological processes, in vivo experiments are required. In cancer translational research and in the development of new therapeutics, many important advances have been accomplished by the use of patient-derived xenografts, that is, patient-derived tumors transplanted in immunocompromised mice17 with the advantage of recapitulating intra- and intertumor heterogeneity.18 However, the absence of an immune system in these mice limits their use to study immune-based treatments.19 With immunotherapy likely being a permanent component of the anticancer arsenal, better in vitro and in vivo preclinical models are needed.20, 21 Ex vivo spheroid models have been generated to screen immunotherapy combinations, but such approach is also limited by lacking the ability to study the tumor–immune system interactions.22 Likewise, the use of syngenic murine-derived cancer models in immune-competent mice is regrettable on the basis of current knowledge of the molecular heterogeneity of human malignancies, limited available models, and differences between mouse and human immunology.23, 24, 25

To gain a better biological understanding of the human immune system, “hematopoietic humanized mice” have been developed. These models provide an opportunity to study the human biological process that would not otherwise be possible.

Currently several humanized mouse models are being used to study human diseases.26 They can be generated by transplantation of (i) human peripheral blood mononuclear cells, (ii) tumor infiltrating lymphocytes, (iii) CD34+ human hematopoietic stem, or (iv) transplantation of human fetal liver and thymus under the kidney capsule and injection of autologous fetal liver human stem cells.27, 28, 29

Because of their immunosuppressed environment, these humanized models have shown to accept allogeneic tumors, providing a novel preclinical platform to study innovative therapeutic combination in cancer.30

These models allow a comprehensive analysis of the human immune system, granting access to lymph nodes, spleen, and tumor tissues and providing more information about immune response. Immunotherapies have started a new era in cancer therapy, but the impressive immune-mediated responses are still limited to a minority of patients. Despite the encouraging results obtained in the clinical setting and the initial evidence of the importance of tumor mutation load and genetic alterations, we still lack the full understanding of mechanisms responsible for tumor immune rejection. Humanized mouse models can improve our knowledge and facilitated testing of novel therapeutic combinations.31

How to measure kidney function in patients with cancer

Measuring glomerular filtration rate (GFR) in patients with neoplasia is fundamental for profiling both the risk and the appropriate dose of chemotherapeutic agents. Ideally GFR should be measured using criterion standard, that is, by chromium-51-ethylenediaminetetraacetic acid (51Cr-EDTA) or technetium-99m–diethylenetriaminepentaacetic acid (99mTc-DTPA) or by inulin or iothalamate clearance32 (see Canadian Cancer Association: Glomerular Filtration Rate study, http://www.cancer.ca). However, these methods are time-consuming and costly. For this reason, in the vast majority of patients with cancer, GFR is estimated by creatinine-based formulas. Several studies in patients with cancer examined the reliability of current creatinine-based methods, namely, the Cockcroft-Gault equation, the 4-variable Modification of Diet in Renal Disease equation based on either uncalibrated creatinine or calibrated creatinine, and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Nevertheless, these studies focused on a specific type of cancer,33, 34, 35, 36 did not test the CKD-EPI equation,37 and included a small number of patients.34, 36 The largest and most thorough study so far, by Janowitz et al.,38 included >2000 patients with various types of cancers. The study tested all main creatinine-based GFR formulas as well as a new Janowitz equation validated against an established criterion standard such as 51Cr-EDTA. The new equation was slightly more precise than the CKD-EPI equation and showed no bias, denoting adequate accuracy.38 A GFR calculator based on the Janowitz equation is available online at http://tavarelab.cruk.cam.ac.uk/JanowitzWilliamsGFR/. For extensive validation in diverse populations and the satisfactory accuracy and precision in patients with cancer, the CKD-EPI formula appears suitable for application in this population. If further validated in other large databases, the new equation38 can emerge as the new standard of care for patients with cancer.

A formula based on the combination of creatinine and cystatin C measurements is the most reliable estimate of GFR in the general population and in patients with CKD,39, 40 but there is no adequate validation study of this formula in the population with cancer. Cystatin C is influenced by inflammation and cell turnover, and in B-cell non-Hodgkin lymphoma its synthesis is increased in immature dendritic cells,41, 42 making this marker a less than ideal GFR surrogate.

Future directions for the direct measurement of GFR in patients with cancer include the development of fluorescence methods for real-time GFR determination.43 Specifically, dextrans of different molecular weight can be labeled by different fluorochromes and thus be used with 2-compartmental models to measure the plasma volume (unfiltered dextrans) and GFR (filtered dextrans). Furthermore, fluorescence could be detected at the level of the skin, thus avoiding taking blood samples. Theoretically, this method could easily and rapidly measure GFR and plasma volume and potentially estimate renal reserve (i.e., the increase in GFR after a protein meal or infusion of amino acids44). This may be particularly useful in allowing for rapid dose adjustments of potentially toxic drugs. However, several questions remain regarding this new technology and it has yet to be implemented in clinical practice.

Cancer in patients with a solid organ transplant

Neoplasia is the third cause of mortality in transplant recipients, and its incidence has been increasing over the past decade.45 These patients have a 3- to 5-fold increased risk of developing solid organ cancers and a 60- to 200-fold increased risk of skin cancers in comparison to the general population.46 Immunosuppressive therapy is the main cause of this dramatic increase. Immunosuppression induces a significant increase in viral infections, and most of the posttransplant neoplasia is well known to be linked to the action of specific viruses.47 In addition, immunosuppressive drugs may have direct effects on the development of particular types of cancer, as demonstrated for azathioprine.48 Finally, immunosuppression can facilitate the process of tumor immune escape. The reduced ability of the immune system to control neoplastic cell growth might also explain the particular aggressiveness of neoplasia in this setting. Indeed, the mortality rate for any specific neoplasia is significantly higher in patients with a transplant than in the general population.49

Given the high risk of neoplasia, prevention should be the main objective of clinical care in this patient population. In this perspective, the first aim is to exclude that either the organ or the patient has an occult neoplasm at transplantation.50 Both donors' and recipients' screening has significantly changed in the last few years, because a general history of neoplasia does not represent per se a contraindication to transplantation, but is considered on a case-by-case basis.50, 51 Screening needs to be expanded to include the whole posttransplant period, aiming for a timely diagnosis, which is particularly relevant.52 Finally, available evidence suggests that in high-risk recipients the use of the mammalian target of rapamycin (mTOR) inhibitor–based immunosuppressive regimen might be beneficial.46, 52

Cancer in patients with CKD

Albuminuria is well recognized as an independent risk factor for cardiovascular disease, especially in patients with diabetes and hypertension.53, 54

Clinical and experimental evidence suggests that endothelial dysfunction, chronic inflammation, and transvascular leakage of macromolecules may be responsible for the association between albuminuria and cardiovascular disease.55, 56 In addition to this well-known connection, emerging evidence indicates that albuminuria is linked to an increased risk of cancer mortality. Studies using data from the Third National Health and Nutrition Examination Survey (NHANES III) demonstrated that albuminuria is associated with an

increased risk of cancer death from all causes, lung cancer, and prostate cancer in men 50 years and older. Interestingly, this association was present only in men, as it was not significant for any type of cancer in women of the same age.57 In addition to this link, several studies have shown that baseline albuminuria is linked to increased cancer incidence. In one of these studies, subjects in the highest quartile of albuminuria were 8.3- and 2.4-fold more likely to receive a diagnosis of bladder and lung cancer, respectively.58

Patients with CKD have a 5- to 15-fold increased risk of cardiovascular mortality.59, 60 In addition, population-based studies have demonstrated that patients with CKD are at a higher risk of cancer, even those with mild to moderate stages of CKD.61 Patients with moderate CKD have an increased risk of cancer mortality, especially those with liver and urinary tract cancer,62 while others have shown that modest reductions in GFR <60 ml/min per 1.73 m2 are linked to an increased risk of cancer death.12 In the latter study, the association between reduced kidney function and cancer death appeared to be specific for breast cancer and urinary tract cancer. Other large longitudinal studies have shown a correlation between the severity of CKD and cancer mortality. Specifically, mortality from liver cancer, kidney cancer, and urinary tract cancer increased incrementally with the severity of CKD.62

These epidemiological data introduce a number of additional topics concerning the difficulties in cancer treatment, screening, and biopsy in patients with CKD. The treatment of cancer is difficult because of the reduced renal excretion of drugs and different pharmacodynamics/pharmacokinetics of anticancer drugs in patients with CKD. For screening cancer in patients with CKD, we rely on standard guidelines for screening in the general population: specific surveillance protocols await further validation, and at present, considerable differences among nephrologists exist.63 Finally, the therapeutic and diagnostic strategies with regard to renal complications in patients with cancer are probably suboptimal at present. Renal biopsy has been recommended in case of glomerular damage (hypertension, edema, proteinuria, and hematuria), interstitial disease (eosinophiluria), vascular disease/vasculitis, or unresolved tubular disease.64

Renal cancer: multidisciplinary treatment approaches

When Robson et al. initially described the management of renal cancer, surgery included the removal of the entire kidney.65 Therefore, surgical extirpation was usually affected by a significant decline in renal function and an increased risk of cardiovascular morbidity. Nowadays, the maximum preservation of normal renal parenchyma is standard of care, when technically feasible.66 Nonetheless, up to 40% to 50% of patients treated with radical nephrectomy and up to 10% to 15% of nephron-sparing surgery cases experience renal functional impairment at 1 year after surgery.67

In cases of metastatic renal cell carcinoma (RCC), systemic therapy has evolved rapidly over the past decade (Table 168, 69, 70, 71, 72, 73, 74, 75, 76, 77). Cytokines have largely been replaced in current practice by tyrosine kinase inhibitors.78 The mammalian target of rapamycin (mTOR) inhibitor therapy is nowadays considered largely inferior to vascular endothelial growth factor (VEGF)–based therapy, although it has a role in combination strategies.78

Finally, vaccines have failed to show an improved survival to date.78 More recently, combination strategies involving contemporary immunotherapy have emerged as key opportunities to further shift the treatment

landscape.78 With the advent of new therapies, median survival for patients with good-to-intermediate- and poor-risk metastatic RCC has increased from 26, 14, and 7 months to 43, 23, and 8 months.78

For all those reasons, functional outcomes, overall survival, and quality of life of cancer survivors gained increasing scientific attention in the past years.79 Efforts have been made to clarify the pathophysiology and mechanisms underlying the development of CKD after nephron-sparing surgery or radical nephrectomy. Beyond the surgical aspects, much more emphasis has been placed to patients' comorbidities and baseline characteristics. That said, a multidisciplinary approach to the decision making in patients with a renal mass may maximize those outcomes (Figure 2). Unfortunately, nowadays such an approach is not pursued in many urological cancer centers. To investigate this aspect, the Kidney Cancer Young Academic Urologists Working party recently promoted an Internet-based survey with the aim to better understand how urologists take care of renal function.80 Although virtually all urologists (98%) answered that renal function is a critical variable for decision making, the consultation of a nephrologist after surgery for a patient with established CKD risk factors is contemplated in merely 17% of the cases. This is even more important if we considered that only a quarter of the urologists acknowledged albuminuria and obesity as key determinants of postoperative CKD. Of note, the latest European guidelines do not suggest referring patients with RCC for a perioperative nephrological assessment. Conversely, the American guidelines recommend nephrology referral after urological treatment, at least when CKD and/or proteinuria is detected.

A multidisciplinary management according to patients' individual risk factors appears mandatory to shift from a purely surgeon-oriented point of view to a holistic consideration to further improve functional outcomes and quality of life of patients with RCC.81, 82

Glomerular diseases associated with cancer

There is a strong association between cancer and glomerulonephritis.83, 84 One study58 found that proteinuria is more frequent in patients with malignancies than in controls. Data from the Danish Kidney Biopsy Register show a higher incidence of cancer in patients with glomerulopathy than in the general population.85

Membranous nephropathy is the most frequent cancer-associated glomerulonephritis.86 The pathogenesis is due to subepithelial deposition of tumor antigens87 associated with an enhanced immune reaction triggered by a malignant tumor.88 Seronegativity to anti-phospholipase A2 receptor antibodies, immunohistochemical identification of IgG1 and IgG2 subclasses,89 and >8 inflammatory cells per glomerulus are the main criteria to differentiate idiopathic membranous nephropathy from cancer-related membranous nephropathy.

Minimal change disease occurs in ∼1% of patients with Hodgkin lymphoma, and the occurrence of focal segmental glomerulosclerosis is about one-tenth that of minimal change disease. Interleukin-13 serum levels seem to play an important role.90 Minimal change disease and focal segmental glomerulosclerosis are also associated with solid tumors. VEGF has been potentially implicated in pathogenesis because of its ability to increase glomerular permeability.91

Rapid progressive glomerulonephritis can develop in patients with RCC, gastric cancer, and lung cancer. Conversely, patients with antineutrophil cytoplasmic antibody–associated (ANCA) vasculitis exhibit a higher risk of a malignant tumor than did the general population.92

Membranoproliferative glomerulonephritis has been associated with solid tumors (lung, renal, and gastric); this is an immune complex disease caused by tumor antigen formation and the inability of the host to effectively clear these antigens.93 It may also develop in the context of chronic lymphocytic leukemia, hairy cell leukemia, and B-cell non-Hodgkin lymphoma.

IgA nephropathy is associated with respiratory tract, oral mucosa, and nasopharyngeal cancer; RCC, and cutaneous T-cell lymphoma. It has been hypothesized that the invasion of the site-specific lymphoid-associated tissue by cancer cells leads to increased circulating levels of IgA because of overproduction of interleukin-6.94

Nephrotoxicity from chemotherapy

Nephrotoxicity of conventional chemotherapeutic agents remains a significant problem in patients with cancer not only because of its impact on the survival of patients with cancer but also because of its dose-limiting effect on the adequate cancer treatment. Although nephrotoxicity is a major side effect of many chemotherapeutic agents, not all patients exposed to these agents develop kidney injury. This suggests the presence of several factors that could increase the patient's risk of nephrotoxicity, including the patient's age, intravascular volume depletion, and the presence of underlying AKI or CKD.95

Conventional cytotoxic agents can cause nephrotoxicity by various mechanisms involving different parts of kidney anatomy including glomerulus, tubules, interstitium, and renal microvasculature with kidney manifestations ranging from an acute interstitial nephritis, focal segmental glomerulosclerosis, and hypertension to various electrolyte disorders, capillary leak syndrome, and thrombotic microangiopathy (TMA).13

Unfortunately, a subset of patients who develop nephrotoxicity can give rise to long-term complications such as chronic interstitial nephritis and CKD.

A major kidney complication of both mitomycin C and gemcitabine, 2 other important conventional chemotherapeutic agents, is the development of TMA. Interestingly, there are often findings of both acute and chronic TMA with these drugs. Whereas acute TMA is characterized by the formation of fibrin microthrombi in arteries, arterioles, and glomerular capillaries, chronic TMA is typically considered as sclerosis and "onion skin" appearance of arteries and arterioles. Mitomycin C–induced TMA is dose dependent,96, 97 whereas no clear relationship has been observed between the cumulative dose of gemcitabine and the risk of TMA. The underlying molecular mechanism of gemcitabine-induced TMA is not well established; it might involve both direct endothelial injury and diminished activity of a von Willebrand

factor named ADAMTS-13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13).98

TMA has also been observed after treatment with VEGF inhibitors (such as bevacizumab) and inhibitors of VEGF tyrosine kinase domain (such as sunitinib).99 These drugs, collectively called VEGF signaling pathway inhibitors, are plagued by an increased risk of cardiovascular disease due to vascular toxicity. Indeed, up to 42% of patients treated with bevacizumab and 34% of those treated with sunitinib develop hypertension (Micromedex and Lexicomp data). It has been even suggested that hypertension could be used as a sign of efficacy of VEGF signaling pathway inhibitors.100 The mechanism of VEGF signaling pathway–induced hypertension is thought to involve nitric oxide regulation at the vascular level and reduced natriuresis at the level of the kidney.100

Overall, a better definition of these interactions and further understanding of the molecular mechanisms whereby cytotoxic agents induce nephrotoxicity could provide better strategies to manage the kidney side effects of cytotoxic agents.

Molecular mechanisms of cisplatin-induced AKI

Cisplatin is an effective chemotherapeutic drug for a broad spectrum of solid organ malignancies. Its main dose-limiting side effect is its nephrotoxicity, which can present in many forms, the most serious and common being AKI.101 In early clinical use, a dose-related incidence of cisplatin-induced AKI was reported in 14% to 100% of patients, which decreased to 20% to 30% more recently with the use of saline hydration and diuresis.102, 103 Diuresis induced by the atrial natriuretic factor was also tested,104 and parathyroidectomy is reported to exert some beneficial action.104, 105

Cisplatin is traditionally believed to exert its antitumor effect through its interaction with DNA, leading to the formation of inter- and intrastrand cross-links, causing DNA synthesis and replication arrest.106 However, recently an important question was raised on why kidney proximal tubular cells (PTCs) with relatively low rates of cell proliferation are especially prone to cisplatin-induced cytotoxicity. One recent persuasive explanation is that nephrotoxicity could result from mitochondrial damage and the release of high levels of mitochondrial reactive oxygen species.107, 108 This hypothesis is reinforced by the finding that along the proximal tubular epithelium, there are 2 membrane transporters that mediate cisplatin uptake in PTCs.109

Cisplatin binds both nuclear and mitochondrial DNA, leading to cell cycle arrest and mitochondrial dysfunction.102 Because of their high-energy functions in active transport,110, 111 PTCs have high mitochondrial density and are particularly susceptible to cisplatin.

Mitochondria are highly dynamic organelles that continuously divide and unite through fission and fusion events to meet cell energy demands.107 There is a large body of evidence demonstrating that NAD+-dependent deacetylase sirtuin 3 (SIRT3) maintains mitochondrial vitality by regulating processes such as energy homeostasis and antioxidant defenses.112, 113

In experimental cisplatin-induced AKI, reduced SIRT3 levels are associated with oxidative stress and mitochondrial damage,114 leading to metabolic and functional impairment of PTCs.114 Mechanistically, cisplatin-induced reduction of SIRT3 levels triggers the upregulation of dynamin-related protein 1 and mitochondrial fission factor and the downregulation of optic atrophy 1, tipping mitochondrial dynamics toward fragmentation, along with loss of mitochondrial membrane potential and organelle disposal.114 The functional role of SIRT3 is highlighted by SIRT3-deficient mice experiencing more severe AKI and dying prematurely after receiving cisplatin.114 In wild-type mice with AKI, treatment with agents that increase SIRT3 expression and activity improves renal function and decrease tubular injury by preventing changes in mitochondrial dynamics.114

Enhancing SIRT3 preserves cellular cytoskeleton integrity, enabling the intercellular transfer of healthy mitochondria via tubulin-rich projections in cisplatin-injured PTCs.115 This reparative dialogue between adjacent PTCs favors bioenergetic cross talk and redox balance, which is abolished by SIRT3 silencing in PTCs.115

The natural outcome of these studies is the search for SIRT3-activating compounds. In this context, honokiol, a biphenolic compound derived from the bark of magnolia trees,116 has been shown to selectively increase SIRT3 and has anti-inflammatory and antioxidant effects.117, 118

Furthermore, NAD+ precursors including nicotinamide, nicotinamide riboside, nicotinamide mononucleotide, or exogenous NAD+ have been found to be beneficial in cardiac and renal diseases119, 120 to the extent that nicotinamide supplementation has been associated with less frequent AKI in hospitalized patients.121

Immunotherapy and interstitial nephritis

Cancer immunotherapy exploits the immune system to fight tumor cells. The availability today of selective immune stimulants has finally solidified the original idea into a therapeutic success. The dark side of immunotherapy is the unavoidable presence of autoimmune effects, such as interstitial nephritis. Specifically, the class of immunotherapy drugs called immune checkpoint inhibitors results in clinically relevant kidney damage in 1% to 3% of patients; however, the percentage of subclinical interstitial nephritis might be much higher, up to one-third of patients with immune checkpoint inhibitors, according to autoptic series.122 Clearly this depends on our limited ability to identify this renal damage with classical blood tests: better biomarkers are thus needed. Immune checkpoint inhibitors could determine interstitial nephritis when T cells are primed by drugs associated with tubular damage, such as proton pump inhibitors and nonsteroidal anti-inflammatory drugs. The treatment is the same as it is for other T cell–mediated kidney injuries (such as after HIV infection and renal allograft rejection) and mostly depends on the use of steroids.123

Electrolyte disorders in patients with cancer

Electrolyte disorders are commonly seen in patients with any form of cancer.124 Table 2 lists the common etiologies of these electrolyte disorders.

Hyponatremia is the most common electrolyte disorder encountered in patients with cancer.125, 126, 127, 128, 129 Hyponatremia is associated with increased mortality and poor response to therapy.129, 130, 131, 132 The syndrome of inappropriate antidiuretic hormone may result from numerous malignancies and numerous chemotherapeutic regimens.133, 134, 135, 136 A diagnosis of hyponatremia may also be a marker of occult neoplasms.137, 138 Treatment of hyponatremia in patients with cancer is challenging and often suboptimal.139 Blockade of the type 2 vasopressin receptor with tolvaptan may be particularly useful in cases of refractory syndrome of inappropriate antidiuretic hormone.140 At least in patients with non–small cell lung cancer, normalization of serum sodium was associated with improved prognosis.141

Hypernatremia is less commonly seen and may be due to malignant involvement of the hypothalamic-pituitary axis or hypercalcemia-induced nephrogenic diabetes insipidus.129, 142 Hypernatremia is associated with substantial mortality risk.143

Hypercalcemia is common in multiple myeloma and advanced stage cancers.144

Survival in patients with cancer-associated hypercalcemia is dismal.145, 146 Hypercalcemia is most often caused by the release of parathyroid hormone–related peptide or local osteolysis (mediated by cytokines) (Figure 3).147, 148, 149, 150, 151 Treatment of cancer-associated hypercalcemia includes intravenous hydration to increase renal calcium excretion, followed by either bisphosphonate, calcitonin, or denosumab, to decrease the bone release of calcium.147, 152

Hypokalemia results from gastrointestinal or renal losses (due to ifosfamide, cisplatin, non-K+–sparing diuretics, or rarely leukemia-associated lysozymuria).129, 133, 153, 154 Hypokalemia may also be caused by the paraneoplastic secretion of ectopic adrenocorticotropin hormone.155, 156 Spurious hypokalemia (pseudohypokalemia) may occur in patients with acute myeloid leukemia and a marked leukocytosis.157

Hyperkalemia may result from tumor lysis syndrome.158, 159 Less common causes include adrenal insufficiency and drugs (calcineurin inhibitors). Of particular importance is pseudohyperkalemia, usually in the setting of marked leukocytosis or thrombocytosis.157

Hypophosphatemia can occur with proximal tubular dysfunction (Fanconi syndrome) because of toxic light chains in multiple myeloma.160 A rare etiology of hypophosphatemia is the syndrome of tumor-induced osteomalacia, in which tumor production of phosphaturic factors, such as fibroblast growth factor 23, results in decreased renal tubular reabsorption of phosphate.161

In patients with multiple myeloma and Waldenström macroglobulinemia, circulating monoclonal proteins can interfere with the laboratory measurement of phosphate, resulting in spuriously elevated serum phosphate levels (pseudohyperphosphatemia).162

Hypomagnesemia can be due to gastrointestinal losses or renal tubular dysfunction due to chemotherapy.163, 164 Chemotherapeutic agents with hypomagnesemia include cisplatin and cetuximab.154, 164

Cannabinoids, endocannabinoids, and cancer

The psychotropic principle of Cannabis sativa, Δ9-tetrahydrocannabinol, and its synthetic derivative, nabilone, are already used for nausea induced by chemotherapeutic agents and have also been suggested to reduce cachexia, another possible consequence of cancer.165 However, the discovery of the mechanism of action of Δ9-tetrahydrocannabinol via 2 G protein–coupled receptors, known as cannabinoid receptor type 1 (CB1) and 2 (CB2), and the fact that these receptors are activated by endogenous lipid mediators, known as endocannabinoids, have opened new therapeutic possibilities for several tumors, beyond merely palliative treatments.166 In fact, the activation of CB1 and/or CB2 by Δ9-tetrahydrocannabinol, endocannabinoids, and several synthetic agonists of such receptors was shown to interfere with the growth of several types of solid tumors, including, but not limited to, breast, prostate, and colorectal carcinomas, glioblastoma, as well as skin cancers, including malignant melanomas in vitro and in vivo, in xenograft as well as genetic experimental models.167 The anticancer action of CB1 and CB2 agonists occurs through several parallel mechanisms, including inhibition of the cell cycle, induction of apoptosis, inhibition of neovascularization, and counteraction of metastatic processes.168 Furthermore, inhibitors of endocannabinoid enzymatic inactivation were shown to be effective and possibly devoid of the unwanted psychotropic effects of CB1 agonists.169 More recently, however, nonpsychotropic cannabinoids that act only in part via the endocannabinoid system and hit several molecular targets have been suggested to be effective anticancer agents.170 Their use as add-on therapies to chemotherapeutic or biological drugs should be considered in future clinical trials.

Future directions and research agenda for onco-nephrology

Onco-nephrology is an emerging and expanding field and, as such, the items to be investigated are numerous. The amount of information is impressive, but this contrasts with our poor understanding of the phenomenon and our limited ability to predict and treat nephrotoxicity.

All nephrologists need to be acquainted with these emerging issues and need to constantly improve their knowledge of the nephrotoxic profile of an increasingly growing number of oncological treatments. In addition, the distinctive issues surrounding the diagnosis and treatment of cancer in patients with kidney disease need additional investigation.

In conclusion, we report a short, nonexhaustive list of subjects for a research agenda, which mirror the topics addressed in the article:

(i) To explore novel methods to rapidly and easily measure GFR in the field of onco-nephrology;

(ii) To institute an international registry of cancer in transplanted patients;

(iii) To understand the higher risk of cancer in CKD, glomerulopathies, and kidney transplant recipients;

(iv) To verify which subpopulations with TMA might gain advantage from the use of eculizumab or other novel therapies;

(v) To study approaches for nephroprotection from chemotherapies such as with cisplatin treatment (see, e.g., inhibitors of dipeptidyl peptidase 4 [DPP-4])171;

(vi) To evaluate new biomarkers for AKI (e.g., neutrophil gelatinase-associated lipocalin [NGAL]) in the field of drug-induced nephrotoxicity and plan possible follow-up protocols; and

(vii) Early identification of immunotherapy-linked nephrotoxicity.

Disclosure

EAJ is a cofounder, stock holder, and chief of the Medical Advisory Board of Goldilocks Inc. MHR is a member of AbbVie Data Safety Monitoring Board, Retrophin Data Safety Monitoring Board, and Baxter consultant. VDM receives research grants from GW Pharmaceuticals. All the other authors declared no competing interests.

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Appendix

List of the International Conference on Onco-Nephrology Participants

The following people attended the International Conference on Onco-Nephrology held on December 7 to 9, 2017, in Naples, Italy: Ariga Akitaka, Berne, Switzerland; Amit Alahoti, Houston, Texas, USA; Todd R. Alexander, Toronto, Alberta, Canada; Lucia Altucci, Naples, Italy; Hatem Amer, Rochester, Minnesota, USA; Vincenzo Barone, Pisa, Italy; Ariela Benigni, Bergamo, Italy; Luigi Biancone, Turin, Italy; Joseph V. Bonventre, Boston, Massachusetts, USA; Giovanni Camussi, Turin, Italy; Anna Capasso, Denver, Colorado, USA; Fortunato Ciardiello, Naples, Italy; Umberto Capitanio, Milan, Italy; Michele Caraglia, Naples, Italy; Giacomo Cartenì, Naples, Italy; Andrés Cervantes, Valencia, Spain; Franco Citterio, Rome, Italy; Laura Cosmai, Milan, Italy; Farhad R. Danesh, Houston, Texas, USA; Bruno Daniele, Benevento, Italy; Antonietta D’Errico, Bologna, Italy; Ferdinando De Vita, Naples, Italy; Vincenzo Di Marzo, Laval, Quebec, Canada; Antonio Ereditato, Berne, Switzerland; Geppino Falco, Naples, Italy; Denis Fouque, Lyon, France; Renato Franco, Naples, Italy; Maurizio Gallieni, Milan, Italy; Giovanni Gambaro, Rome, Italy; Loreto Gesualdo, Bari, Italy; Giuseppe Grandaliano, Foggia, Italy; Calvin Kuo, Stanford, California, USA; Edgar A. Jaimes, New York, New York, USA; Vincent Launay-Vacher, Paris, France; Evaristo Maiello, San Giovanni Rotondo, Italy; Francesca Mallamaci, Reggio Calabria, Italy; Jolanta Malysxko, Bialystok, Poland; Gennaro Marino, Naples, Italy; Erica Martinelli, Naples, Italy; Giuseppe Matarese, Naples, Italy; Takeshi Matsubara, Kyoto, Japan; Piergiorgio Messa, Milan, Italy; Carlo Messina, Milan, Italy; Vincenzo Mirone, Naples, Italy; Floriana

Morgillo, Naples, Italy; Alessandro Nanni Costa, Rome, Italy; Michele Orditura, Naples, Italy; Antonello Pani, Cagliari, Italy; Mark Anthony Perazella, New Haven, Connecticut, USA; Alessandra Perna, Naples, Italy; Claudio Pisano, Ariano Irpino, Italy; Todd Pitts, Denver, Colorado, USA; Camillo Porta, Pavia, Italy; Giuseppe Procopio, Milan, Italy; Qi Qian, Rochester, Minnesota, USA; Giuseppe Remuzzi, Bergamo, Italy; Pierre Ronco, Paris, France; Mitchell H. Rosner, Charlottesville, Virginia, USA; Domenico Russo, Naples, Italy; Lilian L. Siu, Toronto, Ontario, Canada; Walter Stadler, Chicago, Illinois; USA; Francesco Trepiccione, Naples, Italy; Teresa Troiani, Naples, Italy; Davide Viggiano, Ariano Irpino, and Alessandro Weisz, Salerno, Italy; Andrzej Więcek, Katowice, Poland; Ding Xiaoqiang, Shanghai, China; Ortensio Zecchino, Ariano Irpino, Italy; Carmine Zoccali, Reggio Calabria, Italy.

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Figure legend

Figure 1. The kidney disease–cancer connection. AKI, acute kidney injury; CKD, chronic kidney disease; ESRD, end-stage renal disorder.

Figure 2. A proposal for a multidisciplinary approach to maximize functional outcomes and quality of life in patients with renal cancer.

Figure 3. Cancer associated with calcium disorders. Both hyper- and hypocalcemia can be associated with an underlying diagnosis of cancer. In each case, specific mechanisms and etiologies are operative. Although hypercalcemia is typically due to the effects of the underlying cancer, hypocalcemia is usually the result of therapeutic maneuvers (surgery, chemotherapies, or radiation therapy). PTH, parathyroid hormone; PTHrP, parathyroid hormone–related protein.

Table 1. First-line setting pivotal trials of targeted systemic therapy in metastatic clear cell renal cell carcinoma[6]

Study	Year	Experimental arm(s)	Control arm(s)	Median overall survival (mo) (HR; 95% CI)
Motzer *et al.*[68]	2007	Sunitinib (n = 375)	IFN (n = 375)	26 vs. 21 (0.82; 0.57–1.00)
Escudier *et al.*[69]	2007	Bevacizumab + IFN (n = 327)	Placebo + IFN (n = 322)	23 vs. 21 (0.86; 0.72–1.04)
Hudes *et al.*[70]	2007	IFN + temsirolimus (n = 210) Temsirolimus (n = 209)	IFN (n = 207)	8 vs. 11 vs. 7 (0.96; 0.76–1.20 and 0.73; 0.58–0.92)
Rini *et al.*[71]	2008	Bevacizumab + IFN (n = 369)	IFN (n = 363)	18 vs. 17 (0.86; 0.73–1.01)
Sternberg *et al.*[72]	2010	Pazopanib (n = 290)	Placebo (n = 145)	23 vs. 20 (0.91; 0.71–1.16)
Motzer *et al.*[73]	2013	Pazopanib (n = 557)	Sunitinib (n = 553)	28 vs. 29 (0.92; 0.79–1.06)
Motzer *et al.*[74]	2013	Tivozanib (n = 260)	Sorafenib (n = 257)	29 vs. 29 (1.24; 0.95–1.62)
Choueiri *et al.*[75]	2018	Cabozantinib (n = 79)	Sunitinib (n = 78)	27 vs. 21 (0.80; 0.53–1.21)
Escudier *et al.*[76]	2017	Nivolumab + ipilimumab (n = 550)	Sunitinib (n = 546)	NR vs. 26 (0.63; 0.44–0.89)
Motzer *et al.*[77]	2018	Atezolizumab + bevacizumab (n = 454)	Sunitinib (n = 461)	NR vs. 26 (0.63; 0.44–0.89)

CI, confidence interval; HR, hazard ratio; IFN, interferon; NR, not reported.