Onco-nephrology: an appraisal of the cancer and chronic kidney disease links

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ABSTRACT

A bidirectional relationship has been observed for kidney disease and cancer. On the one hand, cancer is an important complication noted in kidney disease as well as a major cause of morbidity and mortality in this group. On the other hand, improved cancer treatment has prolonged survival, but also increased the development of acute and chronic kidney disease. The combination of cancer and kidney disease makes it challenging for clinicians to provide comprehensive and safe therapies for this group of patients. As such, clinicians caring for this group must develop expertise and become competent in the practice of a newly evolving subspecialty of nephrology known as ‘onco-nephrology’. This brief narrative review will focus on the cancer risk in patients with underlying kidney disease, the influence of underlying cancer on therapies such as erythropoiesis-stimulating agents (ESAs) and the appropriate dosing of commonly employed anti-neoplastic agents in patients with underlying kidney disease.

Keywords: albuminuria, cancer, dosage adjustment, erythropoiesis-stimulating agents, kidney disease

INTRODUCTION

Cancer is becoming increasingly recognized as a complication and a major cause of morbidity and mortality in the chronic kidney disease (CKD) population. In addition, dramatic progress in therapy of cancer with an associated improvement in survival has made kidney disease a growing concern in this population. The combination of cancer and kidney disease also influences therapies used for both disease processes. Thus, there is a bidirectional relationship between kidney disease and cancer (Figure 1). As such, clinicians caring for patients with this combination of disease must develop expertise and become competent ‘onco-nephrologists’. This brief commentary will focus on the cancer risk in patients with underlying kidney disease, the influence of underlying cancer on therapies such as erythropoiesis-stimulating agents (ESAs) and the appropriate dosing of commonly employed anti-neoplastic agents in patients with underlying kidney disease.

First, we must evaluate the actual significance of the cancer risk in patients with underlying kidney disease. Large observational studies have consistently shown a 2- to 3-fold increased risk of cancer among kidney transplant recipients [1–6] and an excess risk of 20–50% for all cancers among people both with early stage CKD and on dialysis [1]. Piselli et al. [7] confirmed the increased risk for cancer following kidney transplant, and also suggested a possible protective effect of mammalian target of rapamycin inhibitors in reducing the frequency of post-transplant cancers. In addition, the relative cancer-specific mortality rate is approximately five to six times greater than the age- and gender-matched general population [8]. Among 19 103 kidney transplant procedures performed in England between April 2001 and March 2012 (median follow-up 4.4 years), 2085 deaths occurred, of which 376 (18.0%) were due to malignancy (crude mortality rate 361 malignancy-related deaths per 100 000 person-years) [9]. Thus, malignancy as a cause of post-kidney transplantation death is common and requires heightened surveillance [9]. In Table 1, we have compiled a list of specific issues of cancer in various degrees of kidney dysfunction (i.e. CKD stages 3–5, dialysis and transplantation) [9–18]. On the other hand, CKD is common in patients with cancer [19] and is suggested to be an independent risk factor for death from cancer by recent studies [12, 20, 21]. The relationship between kidney disease and cancer is multiple.

Magee [22] has elegantly emphasized the various links between the kidney and cancer. First, cancer and CKD may have the same cause, that is, analgesics and herbal nephrotoxins induce interstitial nephritis and urothelial cancers; HCV infection causes liver cancer and membranoproliferative disease (MPGN), and smoking exposes to bladder/kidney cancer and renovascular disease. Secondly, some kidney diseases may be related to cancer, mainly membranous nephropathy,
minimal change disease, crescentic GN and thrombotic microangiopathy. Thirdly, underlying CKD often limits treatment options or diagnosis of cancer [22]. Examples include the inability of patients to receive and withstand aggressive cancer therapies and/or undergo unclear optimal dosing chemotherapy regimens. In addition, there is concern over multiple and, at times serious drug–drug interactions, as well as exposure to potentially nephrotoxic–iodinated contrast media and multiorgan toxic gadolinium as manifested by nephrogenic systemic fibrosis [22]. This multifaceted link between cancer and kidney disease can ultimately impact on the survival of both CKD and cancer.

As seen with the patients who fall into the CKD definition, albuminuria, also, appears to be an independent risk marker for cancer incidence [21] and cancer deaths [23]. It is uncertain whether the poor survival in people with CKD and cancer is due to a more aggressive form of cancer, ineffective treatment of the underlying malignancy for the reasons stated above, a greater competing risk of death from CKD-related comorbidities or some combination of these factors [24].

**CKD AS AN INDEPENDENT RISK FACTOR FOR DEATH FROM CANCER**

**Albuminuria and cancer**

Albuminuria may reflect a paraneoplastic renal disease and/or may be a marker of cancer incidence and associated mortality (Table 2) [25–32]. Increased urinary albumin/creatinine ratio (UACR) and cancer risk appear to mirror the results of studies of individuals on dialysis, who have higher cancer rates than the general population [4, 33]. The Tromsø study showed that elevated UACR at baseline was correlated with subsequent cancer incidence. A total 590 of 5425 participants without diabetes mellitus or previous cancer had the first diagnosis of cancer at 10.3 years of follow-up. Each standard deviation higher rise in the logarithmically transformed UACR was associated with a relative risk (RR) of 1.17 for cancer (P < 0.001). Independently from smoking, participants with UACR in the highest quintile were 8.3- and 2.4-fold more likely to receive a diagnosis of bladder and lung cancer, respectively [21].

Albuminuria was also associated with an increased risk of cancer deaths from all-cause, lung and prostate cancers in men aged 50 and older in the USA [23]. Report from the Third National Health and Nutrition Examination Survey (NHANES III, 1988–94) found an increased mortality risk associated with logarithmically transformed UACR for all-cause cancer (RR, 1.20), lung cancer (RR, 1.22) and prostate cancer mortality (RR, 1.40) in men. No mortality association between UACR and cancer was apparent in women. In the Prevention of Renal and Vascular End-Stage Disease (PREVEND) study, a 2-fold increase of albuminuria was associated with a 29% increased risk of CVD mortality and a 12% increased risk of non-CVD mortality in the general population, which was attributed primarily to malignant neoplasms [34]. In contrast, a study from Norfolk [35] did not find an association between albuminuria and cancer. Despite the growing recognition for albuminuria as a paraneoplastic and inflammatory phenomenon,
the underlying mechanisms for the association between albuminuria and cancer incidence and mortality are largely unknown [35–38]. One may speculate that the renin–angiotensin system may participate in generating the increased cancer risk associated with albuminuria. Angiotensin II has been implicated in the development or invasion of several kinds of cancer [39]. Angiotensin could exert mitogenic activity through the angiotensin II type I (ATII-I) receptors, whose receptor expression is higher in cancerous prostate [40].

Kidney disease and cancer

As with albuminuria, end-stage renal disease (ESRD) is also a predictor of non-cardiovascular mortality [20], which is related to increased cancer risk attributed to kidney and urinary tract cancer [41–44]. An increased rate of incidence of thyroid cancer, other endocrine cancers, virus infection-related cancers, skin cancer and liver cancer has also been reported in ESRD patients [4, 45, 46]. However, this excess cancer risk in men with CKD does not appear to be limited to those with ESRD or with a transplant, but is also described in those with moderate CKD (Table 2). Wong et al. [24] reported an increased incidence rate of lung cancer and urinary tract cancer among at least Stage 3 CKD patients in a prospective, population-based cohort study and the excess risk began at an estimated GFR (eGFR) of 55 mL/min/1.73 m² (adjusted hazard ratio [HR]) and increased linearly as GFR declined. For every 10-mL/min/1.73 m² decrement in eGFR, the risk for cancer increased by 29% (adjusted HR 1.29), with the greatest risk at an eGFR of <40 mL/min/1.73 m² (adjusted HR 3.01).

Recently, iff et al. [30] also reported that, in older people, eGFR <60 mL/min/1.73 m² is associated with an increased risk of cancer death with a linear relationship between reduction in eGFR and incidence of cancer-specific mortality, independent of age, smoking status, sex, blood pressure as well as serum fibrinogen and fasting blood glucose levels. The association between reduced kidney function and cancer death also appears to be site-specific for breast cancers (2-fold higher) and cancers of the urinary tract system (2.5-fold higher) [30].

### Table 1. Specific issues of cancer in various degrees of kidney dysfunction

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study source</th>
<th>n</th>
<th>Follow-up (median, years)</th>
<th>Death</th>
<th>Common site of malignancy and comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>CKD 3–5 stages</td>
<td>Chinese prospective cohort study</td>
<td>739</td>
<td>4.5</td>
<td>18</td>
<td>35.7</td>
</tr>
<tr>
<td>Dubose et al.</td>
<td>Case-matched, retrospective review of a prospectively maintained database of Louisiana</td>
<td>1223</td>
<td>5</td>
<td>Five-year OS, 75% (CKD) versus 85% (non-CKD), P = 0.47; 5-year DFS, 64% CKD versus 81% (non-CKD), P = 0.45</td>
<td>Study on breast cancer. CKD does not appear to have a significant impact on outcomes in patients with breast cancer</td>
</tr>
<tr>
<td>Weng et al.</td>
<td>Four health screening centres in Taiwan</td>
<td>123 717</td>
<td>7.06</td>
<td>2710</td>
<td>41.2</td>
</tr>
<tr>
<td>Dialysis</td>
<td>Registre REIN</td>
<td>63 311</td>
<td>9</td>
<td>21 818</td>
<td>10.5</td>
</tr>
<tr>
<td>Rosa-Diez et al.</td>
<td>RLADTR</td>
<td>543 669 000</td>
<td>20</td>
<td>NA</td>
<td>1642</td>
</tr>
<tr>
<td>Webster et al.</td>
<td>Australia and New Zealand</td>
<td>15 185</td>
<td>7.2</td>
<td>NA</td>
<td>1642</td>
</tr>
<tr>
<td>Kiberd et al.</td>
<td>French single-centre experience</td>
<td>240</td>
<td>20</td>
<td>NA</td>
<td>16 cancers, mortality rate of 25%</td>
</tr>
<tr>
<td>Koukourgianni et al.</td>
<td>Chinese prospective cohort study</td>
<td>240</td>
<td>20</td>
<td>NA</td>
<td>1642</td>
</tr>
<tr>
<td>Ma et al.</td>
<td>Australian and New Zealand</td>
<td>7040</td>
<td>4.4</td>
<td>NA</td>
<td>468 due to cancer (6.6%)</td>
</tr>
<tr>
<td>Farrugia et al.</td>
<td>English retrospective observational cohort study</td>
<td>19 103</td>
<td>4.4</td>
<td>2085</td>
<td>18.0</td>
</tr>
</tbody>
</table>

CKD, chronic kidney disease; NA, not available; OS, overall survival; DFS, disease-free survival; PTLPD, post-transplantation lymphoproliferative disease; RLADTR, Latin American Dialysis and Renal Transplant Registry; USRDS, United States Renal Data System (between January 1990 and December 2004).
<table>
<thead>
<tr>
<th>Authors</th>
<th>Study design (n)</th>
<th>n (age, years)</th>
<th>Follow-up (years)</th>
<th>Definition</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yuyun et al. [25]</td>
<td>Prospective population-based cohort study EPIC-Norfolk</td>
<td>20 911 (40–79)</td>
<td>Average, 6.3</td>
<td>UACR</td>
<td>Increased mortality rate across categories of albuminuria and CVD and non-CVD only significant in men.</td>
</tr>
<tr>
<td>Fried et al. [20]</td>
<td>Prospective community-based cohort study from the ACHS</td>
<td>4637 (74 ± 5)</td>
<td>9.5</td>
<td>Cystatin C and eGFR UACR</td>
<td>Higher (19.9 versus 13.9/1000 patient-years) unadjusted rates of death secondary to cancer in older patients with CKD than those without CKD.</td>
</tr>
<tr>
<td>Jørgensen et al. [21]</td>
<td>Population-based longitudinal study, Tromsø study</td>
<td>5425</td>
<td>10.3</td>
<td>UACR</td>
<td>Correlation between baseline ACR and incidence of cancer Compared with lowest UACR quintile, participants with ACR in the highest quintile were 8.3- and 2.4-fold more likely to receive a diagnosis of bladder cancer and lung cancer, respectively.</td>
</tr>
<tr>
<td>Wong et al. [24]</td>
<td>Prospective-based cohort study from the BMES and NSWCR, Australia</td>
<td>3654 (49–74)</td>
<td>10.1</td>
<td>eGFR</td>
<td>Moderate CKD (eGFR of 55 mL/min) increases the risk for all cancers in men by 40%. For every 10-mL/min decrement in eGFR, the risk for cancer increased by 29%. Increased mortality risk associated with UACR for all cancer [RR, 1.20; 95% CI 1.06–1.36], lung cancer [RR, 1.22; 95% CI 1.05–1.43] and prostate cancer mortality [RR, 1.40; 95% CI 1.01–1.95] in men only.</td>
</tr>
<tr>
<td>Lin et al. [23]</td>
<td>Prospective-based NHANES III (1988–94)</td>
<td>6112 (≥50)</td>
<td>12.4</td>
<td>UACR</td>
<td></td>
</tr>
<tr>
<td>Weng et al. [12]</td>
<td>Population-based longitudinal study from Taiwan</td>
<td>123 717 (61 ± 11.9)</td>
<td>7.06</td>
<td>eGFR/MDRD</td>
<td>Significant graded relationship between the severity of non-dialysis-dependent CKD and cancer mortality. 26 and 36.4% had CKD defined by albuminuria or eGFR &lt;60 mL/min/1.73 m² and cancer, respectively.</td>
</tr>
<tr>
<td>Whaley-Connell et al. [26]</td>
<td>Prospective study, Database from NKF KEEP</td>
<td>109 285 (63 ± 14.5)</td>
<td></td>
<td>Albuminuria and eGFR CKD EPI</td>
<td></td>
</tr>
<tr>
<td>Christensson et al. [27]</td>
<td>Prospective population-based cohort study</td>
<td>24 552 (26–61)</td>
<td>28</td>
<td>CKD EPI</td>
<td>Significant association between moderate CKD and kidney cancer risk in younger men (HR, 3.38; 95% CI 1.48–7.71; P &lt; 0.004). ESRD patients with secondary HPT have a 10.2-fold higher risk of developing thyroid cancer than ESRD patients without secondary HPT.</td>
</tr>
<tr>
<td>Lin et al. [28]</td>
<td>Population-based retrospective cohort study Taiwan</td>
<td>1 million</td>
<td></td>
<td></td>
<td>Incidence ratio of renal cancer was higher in lithium-treated patients compared with the general population: 7.51 (95% CI 1.51–21.95) and 13.69 (95% CI 3.68–35.06) in men and women, respectively.</td>
</tr>
<tr>
<td>Zaidan et al. [29]</td>
<td>Retrospective French cohort study from 1996 to 2011</td>
<td>170</td>
<td>Mean lithium exposure, 21.4 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iff et al. [30]</td>
<td>Prospective population-based cohort study from the BMES</td>
<td>4077 (49–97)</td>
<td>Median, 12.8 (8.6–15.8)</td>
<td>eGFR</td>
<td>For every 10-mL/min/1.73 m² reduction in eGFR, an increase in cancer-specific mortality of 18% (P &lt; 0.001).</td>
</tr>
<tr>
<td>Nakamura et al. [31]</td>
<td>Retrospective Japanese cohort study</td>
<td>231 (63.6 ± 12.7)</td>
<td>1</td>
<td>MDRD</td>
<td>Increased mortality in patients with CKD (HR 14-fold higher) than in those without CKD. CKD was associated with an increased risk of death in cancer patients: eGFR stage III, adjusted HR 1.12 (95% CI 1.01–1.26, P = 0.04); eGFR stage IV–V, adjusted HR 1.75 (95% CI 1.32–2.32, P &lt; 0.001).</td>
</tr>
<tr>
<td>Na et al. [32]</td>
<td>Retrospective Korean cohort study</td>
<td>8223</td>
<td>1</td>
<td>eGFR</td>
<td></td>
</tr>
</tbody>
</table>

EPIC: Norfolk, European Prospective Investigation into Cancer; Norfolk Cohort; CVD, cardiovascular disease; non-CVD, non-cardiovascular disease; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; UACR, urinary albumin/creatinine ratio; NHANES III; RR, relative risk; MDRD, Modification of Diet in Renal Disease; NKF KEEP, National Kidney Foundation’s Kidney Early Evaluation Program; ACHS, American Cardiovascular Health Study; BMES, Blue Mountain Eye Study; NSWCR, New South Wales Cancer Registry; HPT, hyperparathyroidism.
In their large and highly representative population-based cohort from a cross-sectional screening programme with a median follow-up of 28 years, Christensson et al. [27] found that the long-term risk of kidney cancer was significantly higher only among younger men with moderately impaired kidney function when compared with those with normal or mild baseline kidney function impairment. However, Wong et al. [24] were unable to find any increased risk among those with stage 2 CKD.

In other studies, an increased incidence and aggressiveness of upper urinary tract urothelial carcinoma, found among CKD patients [47, 48], was observed with analgesic nephropathy and Chinese herb nephropathy (aristolochic acid nephropathy) [49, 50]. In a retrospective French study, the standardized incidence ratio of renal cancer was significantly higher in long-term lithium-treated patients when compared with the general population: 7.51 and 13.69 in men and women, respectively [29]. In their population-based retrospective cohort consisting of original claim data of 1 million beneficiaries randomly sampled from the Taiwan National Health Insurance Research Database (NHIRD), Lin et al. [28] observed that ESRD patients with secondary hyperparathyroidism exhibited a 10.1-fold increased risk of thyroid cancer than did ESRD patients without this parathyroid complication, after adjusting for comorbidities.

In a longitudinal population-based prospective cohort focusing on cancer-related deaths in Taiwan, a significant graded relationship between the severity of CKD and cancer mortality was found when compared with non-CKD patients. Deaths from cancer of the liver, kidney and urinary tract increased incrementally with the severity of renal impairment with an adjusted HR of 1.74, 3.3 and 7.3, respectively [12].

Continued research on this subject is required to tease out the relative higher incidence and mortality of cancers in CKD patients [22]. Pending this information, we must apply common sense strategies to reduce cancer death risk in CKD patients such as smoking cessation, exclude or limit the use of potential carcinogenic drugs (e.g. cyclophosphamide) and judicious screening for cancers [22]. In light of this sentiment, the use of ESAs in this population will be examined next.

ESAs and Cancer

Anaemia and ESAs in oncology

Approximately 32% of cancer patients present with anaemia at diagnosis and ~54% of initially non-anaemic cancer patients develop anaemia during treatment [51, 52]. In those patients, anaemia can be a result of underlying disease (cancer-related anaemia) or chemotherapy-induced anaemia (CIA) [53]. Clinicians should carefully evaluate the impact of anaemia on quality of life [54] as well as its association with shorter overall survival [55].

ESAs are approved in the USA and Europe for treating CIA based on randomized, placebo-controlled trials, showing that these drugs reduce red blood cell transfusions. Three different ESAs are available to date: epoetin α (Procrit®, Johnson & Johnson; Epogen®, Amgen), epoetin β (NeoRecormon®, Roche) and darbepoetin α (Aranesp®, Amgen). Other novel molecules such as the continuous erythropoietin receptor activator [56, 57] and biosimilars that have been developed [58, 59] are available. More than 80 randomized controlled trials (RCTs) and 20 meta-analyses and systematic reviews on the effects of ESAs in cancer patients have been published [60]. Although ESAs continue to be indicated for the management of CIA, their use in clinical practice has become controversial. ESA safety issues include thromboembolic events [61, 62] and concerns regarding whether ESAs increase disease progression and/or mortality in cancer patients [61–66].

Disease progression and/or mortality in oncology

The ESA-product labelling describes eight clinical trials of concern that suggest ESA use increases disease progression and/or mortality in cancer patients [67–74]. Two studies were performed in the non-indicated setting of radiotherapy treatment only [69, 71], two in the non-indicated anaemia-of-cancer setting (patients received neither chemotherapy nor radiotherapy) [68, 73] and four in the indicated chemotherapy setting [69, 70, 72, 74]. Although the ENHANCE and DAHANCA-10 trials suggested that ESA use increases disease progression, this finding was not replicated in two RCTs in the radiotherapy setting for the treatment of patients with head-and-neck cancer; the Radiation Therapy Oncology Group (RTOG 99-03) trial [75] and the controlled EPO-GBR-7 trial [76]. Nonetheless, based on the ENHANCE and DAHANCA-10 studies, the ESA-product labelling does not recommend ESA use in the radiotherapy-only setting. Hence, several meta-analyses of RCTs exploring the risk of worsening the life prognosis for cancer patients on ESA were reported [61–66, 77–81]. The majority of the clinical trials reviewed in these meta-analyses were conducted with haemoglobin (Hb) concentrations higher than the accepted standard stated in the current package inserts of ESA in the USA and the EU (Hb concentrations at the beginning of ESA therapy to be 10 g/dL or lower, and target Hb concentration of 10–12 g/dL) and/or clinical trials were conducted in patients not receiving chemotherapy. However, large RCTs reported more deaths in ESA patients compared with controls in various clinical settings, that is head-and-neck cancers undergoing radiotherapy [69, 71], metastatic breast cancer undergoing chemotherapy [69] and advanced stage cancers not receiving chemotherapy [73]. As a result, an increased risk to death cannot be excluded in ESA-treated cancer patients. Two large RCTs to determine the effects of ESAs on overall and progression-free survival in patients with Hb levels of <110 g/L are currently underway [82, 83] and will provide a definitive answer to this important question. Pending the outcome of these two studies in progress, the clinician should refer to the International recommendations for the treatment of chemotherapy-induced anaemia [84–88].

ESA use and cancer risk in CKD

Data on CKD patients with cancer and ESA use are scant. In the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) [89], more than 4000 patients with Type 2 diabetes mellitus and CKD stage 3/4 were randomly assigned to darbepoetin α to achieve an Hb level of 13 g/dL or to...
placebo. Although there was no significant difference in patients reporting a cancer-related adverse event [darbepoetin α group 6.9% and placebo group 6.4% (P = 0.53)], a trend towards an increased risk of death attributed to cancer [darbepoetin α group, 39 deaths; placebo group, 25 deaths (P = 0.08)] was noted. However, the pre-specified secondary analyses showed a higher risk of cancer-related death in patients with a malignancy present at least 5 years prior to randomization (14 of 188 in the darbepoetin group versus 1 of 160 in the placebo group, P = 0.002) [90]. An observational study also showed an increased incidence of stroke or thromboembolic events in CKD patients with cancer, who, however, received two to four times higher doses of ESA compared with those without cancer [91]. In contrast, a Japanese study in CKD stage 4/5 patients failed to show an increased incidence of cancer with ESA therapy [92]. Cancers were reported in 2.7% (101/3762) and 2.4% (88/3653), and annualized event rates were 5.3 and 4.8%, respectively. However, lower Hb average (10.1 g/dL) and short surveillance times limited the study results [91].

### Venous thromboembolic events

Owing to the hypercoagulable state of malignancy, cancer patients are at an increased risk to develop thromboembolic events. Nevertheless, it appears to be a rare event. Data for venous thromboembolic events (VTEs) are available from about 50 RCTs comparing ESA with no ESA treatment in cancer patients, and evaluated in nine meta-analyses [61, 62, 66, 77, 78, 93–96]. Although limitations and potential biases exist, meta-analyses on epoetin β (seven trials including 2112 patients) [95] and darbepoetin α (12 trials including 2297 patients) [96] suggest an increased risk for VTEs in cancer patients.
patients receiving ESAs. In these trials, RR for VTEs was 1.62 [95] and 1.57 [96], respectively. ESAs have the potential to increase thrombogenic activity either by augmented haemoglobin levels through changes in rheology or other mechanisms such as increased or enhanced platelet function. Healthy volunteers receiving recombinant ESAs demonstrate increased platelet reactivity and endothelial activation [97]. Unproven hypotheses are that ESAs could increase the incidence of VTEs by stimulating platelet production [98–103] or by an association between VTEs and JAK2 kinase activation [104]. Physicians treating cancer patients with ESAs might be more aware of the complication of VTEs in patients receiving ESAs.

### CHEMOTHERAPY DOSAGE ADJUSTMENT IN CKD

Anti-cancer drugs can be eliminated primarily by renal and/or non-renal pathways, which are defined as the fraction eliminated via a renal route <15%. One of the important drug-related problems in patients with renal impairment is inappropriate medication use and dosing errors [105, 106]. Along this line, many cytotoxic drugs and their active/toxic metabolites are eliminated through the kidney depending on how much of the substance undergoes renal filtration, tubular secretion and/or tubular reabsorption. Hence, patients with both acute kidney injury (AKI) and CKD receiving chemotherapeutic agents often possess alterations in their pharmacokinetic parameters such as drug absorption, distribution, protein binding, biotransformation and renal excretion, which may result in the accumulation of potentially toxic components and over-dosage [107]. Therefore, clinicians must be wary to appropriately adjust doses of drugs that are excreted primarily by the kidneys. This requires dosing according to the calculated or measured creatinine clearance or eGFR formulas, which will allow the safe use of chemotherapy in patients with underlying kidney disease. Table 3 summarizes the dosage adjustment of the most commonly used chemotherapeutic agents for which dose modification may be required in the setting of underlying kidney disease [108–110].

Importantly, CKD alters also the pharmacokinetics of drugs that are cleared by non-renal mechanisms since it has been shown that uraemia (both AKI and CKD) affects hepatic drug metabolism and coupled transport. Therefore, it will be a challenge for clinicians to prescribe some drugs and develop a rational strategy for drug dosing in the CKD population [111]. Indeed, uraemic toxins interfere with transcriptional activation, cause down-regulation of gene expression mediated by proinflammatory cytokines and directly inhibit the activity of the cytochrome P450s and drug transporters [112]. As of now, the clinician will need to watch for signs of over-dosage and toxicity when the patient appears to have had appropriate ‘renal’ dosing of their chemotherapeutic regimen. Thus, special considerations should be taken when these drugs are prescribed to CKD patients to optimize exposure to cytotoxic drugs and to reduce the risk of adverse effects [110]. Such precautions include the use of less nephrotoxic agents and documented preventive measures, which are well integrated into oncology practice as well as vigilant surveillance [111–113].

### CONCLUSION

Kidney disease and cancer are intertwined in many ways. Underlying kidney disease appears to increase cancer risk and its associated morbidity and mortality. Improved treatment of many malignancies has also extended life with kidney disease as an unfortunate but not necessarily unexpected consequence. This bidirectional relationship has created a clinical challenge for nephrologists as they strive to provide comprehensive and safe management of these patients. This requires that nephrology fellowship training programmes and nephrology societies provide education and updates on the management of this group of patients. This will allow clinicians to develop expertise and competence as ‘onco-nephrologists’ practicing in this new and exciting territory. We are hopeful that this paper starts this educational mission by briefly reviewing cancer risk in patients with underlying CKD, the therapies such as the ESAs on cancer progression and other outcomes, and the appropriate dosing of anti-cancer agents in patients with kidney disease.

### CONFLICT OF INTEREST STATEMENT

None declared.

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C h r o n i c k i d n e y d i s e a s e a n d c a n c e r 1987
Vitamin D analogues to target residual proteinuria: potential impact on cardiorenal outcomes

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ABSTRACT

Residual proteinuria, the amount of proteinuria that remains during optimally dosed renin-angiotensin-aldosterone system (RAAS) blockade, is an independent risk factor for progressive renal function loss and cardiovascular complications in chronic kidney disease (CKD) patients. Dual RAAS blockade may reduce residual proteinuria but without translating into improved cardiorenal outcomes at least in diabetic nephropathy; rather, dual RAAS blockade may increase the risk of adverse events. These findings have challenged the concept of residual proteinuria as an absolute treatment target. Therefore, new strategies must be explored to address whether by further reduction of residual proteinuria using interventions not primarily targeting the RAAS benefit in terms of cardiorenal risk reduction would accrue. Both clinical and experimental intervention studies have demonstrated that vitamin D can reduce residual proteinuria through both RAAS-dependent and RAAS-independent pathways. Future research should prospectively explore vitamin D treatment as an adjunct to RAAS blockade in an interventional trial exploring clinically relevant cardiorenal end points.

Keywords: cardiovascular disease, chronic kidney disease, proteinuria, vitamin D

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