

# Considering renal risk while managing cancer

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**Abstract:** Renal function is an important consideration in the management of patients with advanced cancer. There is a reciprocal relationship between cancer and the kidney: chronic kidney disease can increase the risk of developing cancer, and patients with cancer often experience renal impairment owing to age, disease-related factors and nephrotoxic treatments. As therapies for cancer continue to improve, patients are living longer with their disease, potentially extending the period over which they are susceptible to long-term complications. Furthermore, secondary symptoms, such as bone metastases or infections, may arise that will require treatment. Certain treatments, including chemotherapy, antibiotics and some bone-targeted agents, are nephrotoxic and may require dose modifications or interruptions to prevent renal injury. Nephrologists should play a key role in the identification and management of renal impairment in patients with cancer. Furthermore, they may be able to provide advice on protecting the kidneys in instances where nephrotoxic agents require dose reductions or interruptions, and when novel therapies or combinations are used. Collaboration between oncologists and nephrologists is important to optimal patient management. This article reviews the relationship between cancer and kidney disease and examines the treatments that may impact kidney function. Considerations for monitoring renal function are also discussed.

**Keywords:** advanced cancer, cancer management, elderly, kidney disease, nephrotoxicity, renal function

## Introduction

Advances in health care and treatment options have increased survival times for patients with different solid tumor types. In the UK and the USA, patients with prostate and breast cancer have an estimated 5-year relative survival rate of 28%–100%<sup>1,2</sup> and 22%–100%,<sup>3,4</sup> respectively, depending on the disease stage at diagnosis. Although the relative survival rate of patients with lung cancer is less than that of those with breast or prostate cancer, up to 49% will survive for 5 years or more.<sup>5–7</sup> The consequences of improved survival include the increased incidence of complications associated with the disease process, such as bone metastases,<sup>8–11</sup> and adverse events that may arise as a result of long-term cancer treatments,<sup>12,13</sup> all of which may increase the risk of renal injury. Kidney function is, therefore, an important consideration when cancer is present, and understanding the connection between the two is important for the optimal disease management. Here, we review the relationship between cancer and kidney disease, and examine the treatments that may impact kidney function. Considerations for monitoring renal function are also discussed.

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## Cancer and kidney disease

Kidney disease frequently coexists with advanced cancer because of their shared risk factors and bidirectional causal mechanisms. The reciprocal relationship between cancer and kidney disease is summarized in Figure 1 and discussed in detail in the following section.<sup>14–16</sup>

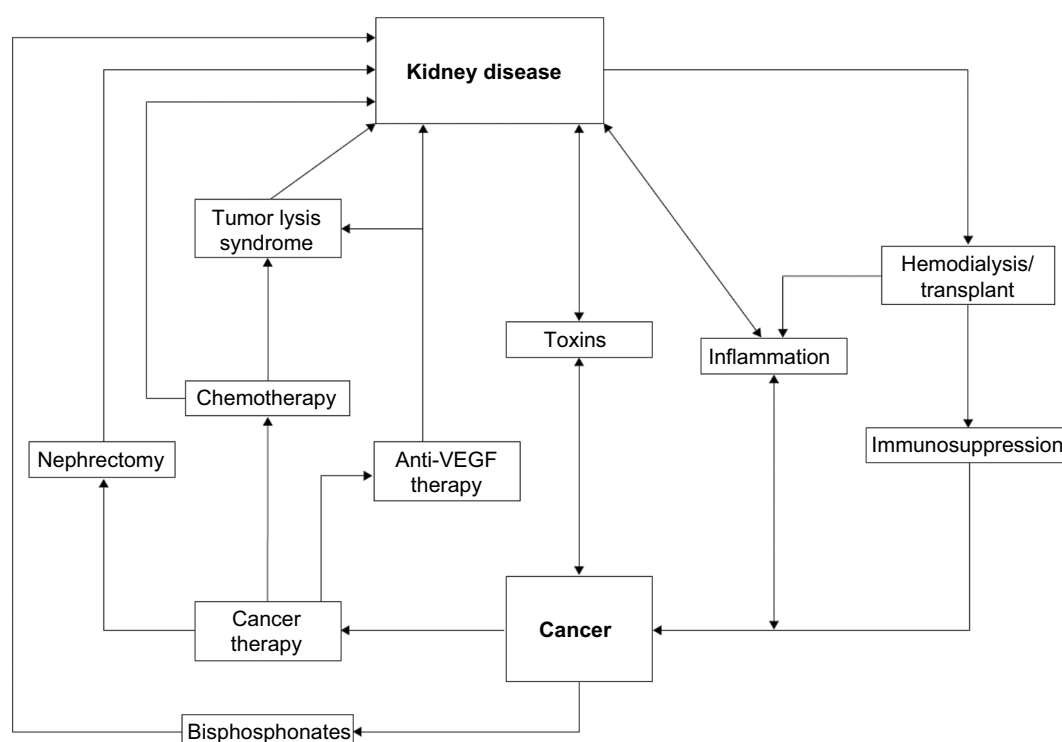
## Diagnosis of kidney disease

Chronic kidney disease (CKD) is usually asymptomatic in the early stages, but can be detected using laboratory tests. Kidney function is commonly assessed by means of the estimated glomerular filtration rate (eGFR). Measurement of serum creatinine levels, in combination with age, sex, weight or race, is used to calculate eGFR. The formal definition of CKD requires the presence of a reduced eGFR of  $<60$  mL/min per  $1.73$  m<sup>2</sup> for at least 90 days.<sup>17</sup> Frequently in the clinical setting, however, a reduced eGFR may be noted on one occurrence without knowledge of its duration – we, hereafter, refer to this as renal impairment (RI), to denote a single reading of eGFR of  $<60$  mL/min per  $1.73$  m<sup>2</sup>, without designation of its chronicity.<sup>18–20</sup>

Two equations are routinely used for the estimation of eGFR based on serum creatinine levels: the Modification of Diet in Renal Disease (MDRD) equation and the recently

developed Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, which may be more accurate than the MDRD equation (Table 1).<sup>20,21</sup> These equations are suitable for use in a broad patient population, including elderly individuals. The Kidney Disease: Improving Global Outcomes (KDIGO) working group does not recommend using one single equation for estimation of renal function, although it recognizes that the CKD-EPI equation may be more precise at higher GFRs and may, therefore, be more applicable than the MDRD equation for day-to-day practice.<sup>18</sup> Historically, creatinine clearance (CrCl) has been used as a marker of GFR and is determined from serum creatinine and urine creatinine levels.<sup>18</sup> Current product labeling guidance from the US Food and Drug Administration (FDA) for studies of patients with impaired renal function states that dose adjustment categories can be described based on CrCl or eGFR.<sup>22</sup>

Measurement of eGFR alone may be insufficient to determine kidney function because there is often a discrepancy between serum creatinine levels and the CrCl rate, and it should, therefore, be used in conjunction with other renal assessments.<sup>23,24</sup> In patients with low body mass index ( $<18.5$  kg/m<sup>2</sup>), such as cachectic patients with cancer, alternative approaches may be used to provide reliable estimates



**Figure 1** The reciprocal relationship between cancer and kidney disease.

**Note:** Data from Stengel B,<sup>16</sup> Akchurin and Kaskel,<sup>42</sup> and Abudayyeh et al.<sup>119</sup>

**Abbreviation:** VEGF, vascular endothelial growth factor.

**Table I** Equations used to estimate GFR

Equation	Notes
<b>Creatinine</b> Cockcroft–Gault <sup>19</sup> $\text{CrCl} = (140 - \text{age}) \times \text{weight (kg)} / 72 \times \text{SCr}$ CrCl = creatinine clearance (mL/min) SCr = serum creatinine (mg/100 mL) CKD-EPI <sup>20</sup> $\text{GFR} = 141 \times \text{minimum (SCr/}\kappa, 1)^\alpha \times \text{maximum (SCr/}\kappa, 1)^{-1.209} \times 0.993^{\text{Age}} \times 1.018$ (if female) or 1.159 (if black) $\kappa = 0.7$ (female) or 0.9 (male) $\alpha = -0.329$ (female) or $-0.411$ (male) minimum = minimum SCr/ $\kappa$ or 1 maximum = maximum SCr/ $\kappa$ or 1 SCr = serum creatinine (mg/dL)  MDRD study equation <sup>18,20</sup> $\text{GFR (mL/min/1.73 m}^2) = 175 \times (\text{SCr})^{-1.154} \times (\text{Age})^{-0.203} \times 0.742$ (if female) $\times 1.212$ (if African-American) SCr = serum creatinine (mg/dL)	Does not estimate GFR          Apply correction factor to GFR values for people of African or Afro-Caribbean descent  Less biased than MDRD at estimating GFR in those with a GFR >60 mL/min/1.73 m <sup>2</sup> Better than MDRD at estimating GFR in patients aged ≥75 years Interpret with caution in patients with extremes of muscle mass May overdiagnose chronic kidney disease May not be accurate for all racial groups
<b>Cystatin C</b> CKD-EPI <sup>18</sup> $133 \times \text{minimum (SCysC/0.8, 1)}^{-0.499} \times \text{maximum (SCysC/0.8, 1)}^{-1.328} \times 0.996^{\text{Age}}$ ( $\times 0.932$ if female) minimum = minimum SCysC/0.8 or 1 maximum = maximum SCysC/0.8 or 1 SCysC = serum cystatin C (mg/L)	More accurate than eGFR of creatinine For confirmatory testing in specific circumstances when eGFR based on serum creatinine is less accurate
<b>Creatinine–cystatin C</b> CKD-EPI <sup>18</sup> $135 \times \text{minimum (SCr/}\kappa, 1)^\alpha \times \text{maximum (SCr/}\kappa, 1)^{-0.601} \times \text{minimum (SCysC/0.8, 1)}^{-0.375} \times \text{maximum (SCysC/0.8, 1)}^{-0.711} \times 0.995^{\text{Age}} \times 0.969$ (if female) or $\times 1.08$ [if black] $\kappa = 0.7$ (female) or 0.9 (male) $\alpha = -0.248$ (female) or $-0.207$ (male) minimum (SCr/ $\kappa$ , 1) = minimum SCr/ $\kappa$ or 1 maximum (SCr/ $\kappa$ , 1) = maximum SCr/ $\kappa$ or 1 minimum (SCysC/0.8, 1) = minimum SCysC/0.8 or 1 maximum (SCysC/0.8, 1) = maximum SCysC/0.8 or 1 SCr = serum creatinine (mg/dL) SCysC = serum cystatin C (mg/L)	More accurate than equations using creatinine or cystatin C separately

**Abbreviations:** CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; SCr, serum creatinine; SCysC, serum cystatin C.

of renal function; for instance, urine CrCl measured over a 24-hour period or cystatin-based measurements.<sup>21</sup> Cystatin C level can be used to estimate GFR; a meta-analysis found it to be superior to using serum creatinine level for this purpose.<sup>25</sup> Although cystatin C measurement may offer some advantages over serum creatinine-based evaluations, the assay can be costly and there is a potential lack of standardization across laboratories. Therefore, the KDIGO working group does not currently recommend use of this assay over serum creatinine-based methods.<sup>18</sup>

Beyond reduction in eGFR, symptoms of kidney disease can include proteinuria, hematuria or albuminuria, or renal

tubular abnormalities leading to electrolyte wasting, all of which can be detected using laboratory tests.<sup>17</sup>

## Risk factors in common for kidney disease and cancer

Age is a major risk factor for kidney disease. Decline of renal function is common in the elderly general population; by the age of 70 years, renal function may have declined by up to 40%.<sup>26</sup> More than a third of individuals in the healthy population aged over 70 years have moderately impaired renal function.<sup>27</sup> The physiological changes associated with aging, including diminished renal mass, reduction in renal

blood flow and loss of nephron function,<sup>28</sup> contribute toward decreased renal activity. Furthermore, as individuals age, they are likely to acquire an increasing number of comorbidities.<sup>29</sup> Thus, it is unsurprising that patients with cancer, who are often elderly, may have some degree of RI.<sup>30,31</sup> In the French Renal Insufficiency and Anticancer Medications (IRMA) national, retrospective, observational study of patients with solid tumors, there was a high incidence of RI (65.2%) in a group of 1553 patients aged  $\geq 65$  years.<sup>31</sup> The prevalence of RI increased with age (65–74 years, 61.7%; 75–84 years, 74.7%).<sup>31</sup> RI occurred frequently in a retrospective study of 11,809 USA patients with bone metastases from solid tumors (mean age 66.9 years); the 5-year prevalence of RI was 43%.<sup>32</sup> In a retrospective study of elderly Brazilian patients (aged  $>65$  years) with solid tumors, 66% were found to have abnormal renal function.<sup>30</sup>

Type II diabetes mellitus is one of the most common causes of kidney disease in the USA and is itself a risk factor for several types of cancer.<sup>15</sup> The association between diabetes and cancer is further complicated by the fact that the majority of patients with diabetes are overweight or obese,<sup>14</sup> which increases their risk of developing several different cancer types<sup>33</sup> and kidney disease.<sup>34</sup> Other identified risk factors for CKD include physical inactivity,<sup>35</sup> smoking, hypertension,<sup>36</sup> cardiovascular disease and being male,<sup>34</sup> all of which pose an increased risk of developing certain cancers.<sup>15</sup>

## CKD as a risk factor for cancer

The relationship between cancer and kidney function encompasses more than age and comorbidities (Figure 1). There is an increased risk of certain cancers in individuals with CKD,<sup>16</sup> and the association is most commonly observed in those with renal cell carcinoma or urothelial cancers.<sup>37</sup> Patients receiving renal replacement therapies, such as dialysis<sup>16,38</sup> or transplantation,<sup>16,39</sup> also have an increased risk of developing cancer. In the UK in 2010, cancer was the most common cause of death in patients who had been given a kidney transplant (23%).<sup>40</sup> Immunosuppression may contribute to an increased risk of cancer, which can be caused by pre- or posttransplantation treatment with immunosuppressants,<sup>41</sup> or by endogenous immunosuppression owing to uremia.

The underlying mechanisms for the association between kidney disease and cancer are not well understood and may be multifactorial. However, CKD can cause an inflammatory microenvironment<sup>42</sup> that may encourage cancer development. Albuminuria, which frequently accompanies inflammatory states, is itself associated with an increased incidence of cancer, in particular urothelial or lung cancer, independent

of renal function.<sup>43</sup> Vitamin D deficiency is highly prevalent among people with moderately reduced kidney function and, in the general population, has been associated with the risk of developing breast, colon and prostate cancer. The mechanisms to explain this association are, however, yet to be elucidated.<sup>44</sup>

## Cancer as a cause of kidney disease

The natural history of cancer may lead to kidney disease via various mechanisms. Acute kidney injury is common in patients with tumors of the kidney or liver, and in those with multiple myeloma,<sup>45</sup> and can be caused by intravascular volume depletion due to sepsis, vomiting or diarrhea, toxins or accumulation of M-protein in multiple myeloma.<sup>46</sup> Physical obstruction of the bladder or urethra, often observed in patients with tumors of the bladder, uterus, prostate and cervix, can also result in acute kidney injury.<sup>46</sup> Nephrotic syndrome may be caused by the invasion of the glomeruli by cancerous cells.<sup>47</sup> Another complication of cancer is tumor lysis syndrome, which results in metabolic disruption and can be caused by rapid tumor cell turnover, or because of chemotherapy-induced cell lysis.<sup>48</sup> Cellular release of metabolites, such as potassium, phosphate and citric acid, can lead to the deposition of uric acid and calcium phosphate in the renal tubules, causing acute renal failure, a condition that is further exacerbated in cases of concomitant intravascular volume depletion.<sup>48</sup>

Patients with advanced cancer often develop bone metastases, particularly those with lung, breast and prostate cancer. Bone metastases disrupt normal bone turnover and can cause an imbalance in calcium levels resulting in hypercalcemia of malignancy, affecting 10%–30% of patients with cancer.<sup>49</sup> Prolonged elevated calcium can cause kidney damage and untreated severe hypercalcemia of malignancy can be fatal.<sup>49</sup>

Hypercalcemia is a key criterion for the diagnosis of multiple myeloma.<sup>50</sup> It is caused by tumor-induced bone destruction and the formation of bone lesions, which together contribute to elevated calcium levels.<sup>51</sup> Furthermore, the clonal expansion of plasma cells and subsequent excessive production of immunoglobulin light chains can cause cast nephropathy, further damaging the kidney.<sup>52</sup>

Given that RI is common in patients with advanced cancer, oncologists need to be aware that certain cancer treatments affect the kidney.<sup>13</sup> These are discussed in detail in the following section.

## Prevalence of kidney disease in advanced cancer

The USA database study found that the 5-year prevalence of RI in patients with solid tumors and bone metastases was

43%, and up to 71% in those with CKD.<sup>32</sup> In the large IRMA study of 4684 patients with a range of solid tumors, over half of patients with breast, prostate or lung cancer had abnormal renal function.<sup>53–55</sup> Renal failure can occur in patients with advanced cancer, affecting 0.4% of women with breast cancer and bone metastases.<sup>55</sup> This is more common in patients with prostate cancer, with one database study reporting that 12% of men with prostate cancer had renal failure in the final year of life.<sup>56</sup>

## Considering renal risk while managing cancer

### Assessing renal risk in patients with cancer

It is reasonable to evaluate renal function in all patients with cancer<sup>23,24,57</sup> because RI has been detected in almost two-thirds of patients with cancer who have normal serum creatinine levels.<sup>24</sup> Given that kidney disease is common in patients with cancer, it is important to understand a patient's renal function in order to assess the risk of further kidney injury that could occur owing to the nephrotoxic effects of some cancer treatments.

Guidelines recommend regular renal monitoring for patients receiving potential nephrotoxic agents.<sup>18,23,58,59</sup> For elderly patients with cancer, the International Society of Geriatric Oncology recommends that renal function should be assessed and hydration should be optimized before drug treatment.<sup>23</sup> The IRMA investigators recommend that CrCl is calculated for patients who are receiving nephrotoxic drugs that require dose adjustments in order that their dosage is prescribed according to patients' levels of renal function. These patients should receive adequate hydration and be monitored closely for a decline in renal function.<sup>23,24</sup> The use of antiresorptive therapies for the management of bone metastases is discussed in detail in the following section.

## Nephrotoxicity associated with the management of cancer

### Diagnosis

Imaging is often used to locate tumors or in the assessment of disease stage. Computed tomography (CT) is the preferred method for identifying renal cell carcinoma and metastases, but is associated with a risk of contrast-induced acute kidney injury, caused by the use of iodinated contrast medium.<sup>60</sup> The incidence of kidney injury in this setting is low in the general population (2%); however, in patients with risk factors for kidney disease it increases up to 50%.<sup>60</sup> Magnetic resonance imaging is often used to detect tumors; although it is less toxic than CT it also carries a potential risk of kidney

injury owing to the use of contrast media often containing gadolinium.<sup>61</sup> Therefore, before renal imaging, physicians should consider a patient's baseline risk of kidney injury and should use prophylaxis with intravenous fluids as an effective intervention. In addition, physicians should consider the use of prophylactic *N*-acetylcysteine, an agent that has been shown to prevent radiocontrast-induced nephropathy.<sup>60</sup>

### Chemotherapy

Most commonly used chemotherapies are excreted through the kidneys and have known nephrotoxicity.<sup>62</sup> Cisplatin is a major antineoplastic alkylating agent used for the treatment of solid tumors. However, acute kidney injury has been reported in 20%–30% of patients receiving cisplatin therapy.<sup>63</sup> The nephrotoxicity associated with cisplatin increases in a dose-dependent fashion<sup>64</sup> and may be managed with amifostine, an agent that protects tissue from chemotherapy-induced damage.<sup>65</sup> Other alkylating agents such as ifosfamide and cyclophosphamide are also nephrotoxic and may have long-term renal effects. For example, survivors of childhood cancers had significantly lower eGFRs in adulthood if they had received high-dose cisplatin (83 vs 101,  $p=0.004$ ) or high-dose ifosfamide (88 vs 98,  $p=0.02$ ) than those who had not received such treatments.<sup>66</sup> Ifosfamide treatment of solid tumors is also associated with long-term nephrotoxicity in adults.<sup>67</sup> Ifosfamide can enter the kidney tubules via organic cation transporters and cause proximal tubular injury. Chloroacetaldehyde is a toxic metabolite of ifosfamide that injures kidney tissue.<sup>62</sup> Owing to differences in metabolism, cyclophosphamide treatment produces much less chloroacetaldehyde and is therefore substantially less nephrotoxic than ifosfamide, although another metabolite, acrolein, can lead to urotoxicity with hemorrhagic cystitis.<sup>62</sup> Beyond those issues, cyclophosphamide has also been rarely associated with the syndrome of inappropriate antidiuresis hormone secretion (SIADH).<sup>62,68</sup> The mechanism of action of cyclophosphamide-related SIADH has not been determined, but it may be caused by a direct toxic effect of cyclophosphamide or its metabolites on renal collecting tubules, or an antidiuretic hormone-like activity of cyclophosphamide metabolites.<sup>68</sup>

Methotrexate is another widely used chemotherapy that is associated with nephrotoxicity.<sup>32</sup> Indeed, up to 12% of patients who received high-dose methotrexate for the treatment of various cancers have experienced acute kidney injury.<sup>62</sup> Furthermore, renal injury can impair clearance of methotrexate, leading to accumulation and further toxicity. Toxicity may be managed using the tissue-protectants leucovorin, or carboxypeptidase-G2, or hemodialysis.<sup>69</sup>



Melphalan is often administered to patients with multiple myeloma, a disease often associated with RI.<sup>70</sup> Melphalan clearance may be decreased in patients with RI and subsequent progression from RI to renal failure has been reported in a patient receiving treatment for multiple myeloma.<sup>71</sup> Dose reductions of 50% are recommended for patients with moderate RI (CrCl 30–50 mL/min) who are not scheduled to receive hematopoietic stem cell transplantation (HSCT), but it should not be used in patients with more severe RI (CrCl <30 mL/min; Table 2).<sup>72</sup> Nonetheless, high-dose melphalan with HSCT has been used successfully in patients with end-stage renal failure who are receiving dialysis.<sup>72,73</sup>

### Antivascular endothelial growth factor receptor therapies

The use of agents that target the vascular endothelial growth factor (VEGF) pathway is increasing in the treatment of certain solid tumors, including renal cell carcinoma, non-small cell lung cancer, gastrointestinal stromal tumors and colorectal cancer.<sup>74</sup> The humanized monoclonal antibody bevacizumab was one of the first VEGF inhibitors to be used in clinical practice for the treatment of solid tumors, but its use is associated with a significantly increased risk of proteinuria and hypertension.<sup>75</sup> In a phase 4, open-label study in patients with lung cancer, grade 3 or higher proteinuria was reported in 3% of patients and hypertension was reported in 6% of patients who received bevacizumab.<sup>76</sup> Other VEGF receptor targets, such as the tyrosine kinase inhibitors sorafenib, sunitinib and pazopanib, are used for the treatment of patients with cancer, but are associated with similar adverse vascular effects.<sup>74</sup> A meta-analysis of 16 clinical trials of patients with solid tumors has shown that the risk of developing proteinuria was 41% higher with the human recombinant fusion protein aflibercept compared with controls; furthermore, this risk was substantially greater with aflibercept than with bevacizumab (85%).<sup>77</sup>

### Immuno-oncology therapies

The immuno-oncology therapies nivolumab and pembrolizumab are monoclonal antibodies that have both recently been approved to treat advanced melanoma.<sup>78,79</sup> Nivolumab is also approved for the treatment of locally advanced or metastatic nonsmall cell lung cancer after prior chemotherapy and as a monotherapy for the treatment of advanced renal cell carcinoma after prior therapy.<sup>78</sup> These compounds are currently under investigation in men with prostate cancer. However, in phase 3 studies, the use of nivolumab monotherapy or nivolumab in combination with ipilimumab is associated

with immune-related nephritis and renal dysfunction (3.2% [55/1728] and 4.2% [19/448], respectively).<sup>78</sup> It is therefore recommended that patients should be monitored for signs and symptoms of nephritis or renal dysfunction. Treatment should be withheld for patients with mild-to-moderate renal dysfunction (from 50% up to 300% increase from a normal baseline serum creatinine) until normalization, with discontinuation recommended in more severe cases.<sup>78</sup> Immune-related nephritis has also been reported for a small number of patients in phase 3 studies receiving pembrolizumab (0.4% [7/1567]); patients should be monitored for changes in renal function, with treatment interrupted or discontinued for indications described above.<sup>79</sup>

### Androgen deprivation therapy (ADT)

ADT is commonly used for the treatment of prostate cancer. However, its use has been associated with an increased risk of acute kidney injury; a large database study calculated an odds ratio of sustaining acute kidney injury of 2.48 (95% confidence interval, 1.61–3.82) with ADT treatment versus controls.<sup>80</sup> ADT may cause dyslipidemia or result in metabolic syndrome, all of which can contribute to kidney injury.<sup>80</sup> Furthermore, patients who received ADT as part of a combination therapy had the highest risk of acute kidney injury, suggesting that ADT may potentiate the nephrotoxicity of other agents.<sup>80</sup>

### Antiresorptive therapies

Bone metastases are common in patients with advanced solid tumors, such as those affecting the breast, prostate or lung (~70%–90% of patients with these cancers have evidence of metastatic bone disease),<sup>11,81</sup> therefore patients may require antiresorptive drugs such as bisphosphonates<sup>82,83</sup> and denosumab,<sup>84–87</sup> for the prevention of skeletal complications of bone metastases secondary to solid tumors.

The use of the bisphosphonate zoledronic acid 4 mg every 3–4 weeks has been associated with a risk of renal deterioration and, in some rare instances, renal failure.<sup>88</sup> However, many patients with kidney disease may be prescribed bisphosphonates, despite the risk of further kidney damage. In a large, retrospective chart review of individuals with bone metastases secondary to solid tumors in the USA, almost half (48%) of patients received bisphosphonates within 12 months of confirmation of CKD.<sup>32</sup> Prescribing information stipulates a reduced dose of zoledronic acid for patients with RI and that creatinine monitoring is recommended before each dose. For patients with severe RI, the use of zoledronic acid is not recommended (Table 2).<sup>88</sup> Despite this, many patients will

**Table 2** Label recommendations for common nephrotoxic agents used in cancer therapy

Drug	Tumor type(s)	Dose adjustment/recommendations
<b>Chemotherapies</b>		
Abiraterone acetate <sup>120</sup>	Castration-resistant prostate cancer	No dose adjustment required for patients with RI. No clinical experience in patients with severe RI and prostate cancer therefore caution is advised
Cisplatin <sup>100</sup>	Testicular, ovarian, bladder and head and neck cancers	Adequate hydration is required before, during and after infusion for patients with RI, especially severe RI Cisplatin is contraindicated in patients with preexisting RI. Nephrotoxicity may be potentiated by aminoglycoside antibiotics
Cyclophosphamide <sup>101</sup>	Hematological malignancies, Ewing's sarcoma, neuroblastoma, ovarian, breast and small cell lung cancers	Adequate hydration is required before, during and after administration. Dose reduction of 50% is recommended for patients with GFR <10 mL/min
Enzalutamide <sup>99</sup>	Castration-resistant prostate cancer	No dose adjustment required for patients with mild or moderate RI (CrCl ≥30 mL/min) Caution is advised in patients with severe RI (CrCl <30 mL/min) or end-stage renal disease
Ifosfamide <sup>102</sup>	Wide range of tumor types	Adequate hydration is required during and after administration Ifosfamide is contraindicated in patients with preexisting RI Dose should be determined and adjusted for each individual, and kidney function should be closely monitored before and after treatment
Methotrexate <sup>103</sup>	Wide range of tumor types	Adequate hydration is required before, during and after administration. Renal function should be closely monitored before, during and after treatment. Dose should be reduced if patients have RI (CrCl 20–50 mL/min) by 50%. Methotrexate is contraindicated in patients with severe RI (CrCl <20 mL/min)
Melphalan <sup>72</sup>	Ovarian cancer and multiple myeloma	A 50% dose reduction is required for patients with moderate RI (CrCl 30–50 mL/min) who are scheduled to receive high-dose melphalan without hematopoietic stem cell rescue. Melphalan should not be used in patients with severe RI
<b>Targeted agents</b>		
Axitinib <sup>121</sup>	Advanced renal cell carcinoma	No dose adjustment is required Virtually no data are available regarding axitinib clearance in patients with CrCl <15 mL/min. Axitinib has not been studied in patients with RI
Bevacizumab <sup>98</sup>	Colorectal, breast, nonsmall cell lung, renal, ovarian and cervical cancers	No trials have been conducted to investigate the pharmacokinetics of bevacizumab in patients with RI because the kidneys are not a major organ for bevacizumab metabolism or excretion. Discontinuation of drug if adverse events are indicated
Pazopanib <sup>107</sup>	Renal cell carcinoma and soft tissue sarcoma	No dose adjustment is required with CrCl >30 mL/min Caution advised in patients with CrCl <30 mL/min
Sunitinib <sup>104</sup>	Gastrointestinal stromal tumor, renal cell carcinoma and pancreatic neuroendocrine tumors	No starting dose adjustments required for patients with RI or end-stage renal disease on dialysis. Subsequent dose adjustments should be based on individual safety and tolerability. Discontinue treatment in patients with nephrotic syndrome
Nivolumab <sup>78</sup>	Melanoma nonsmall cell lung cancer and advanced renal cell carcinoma	No dose adjustment is required for patients with mild or moderate RI Treatment should be permanently discontinued for patients with grade 4 creatinine elevation
Pembrolizumab <sup>79</sup>	Melanoma	No dose adjustment is required for patients with mild or moderate RI Treatment should be permanently discontinued for patients with grade 3 or 4 nephritis
<b>Bone-targeted agents</b>		
Zoledronic acid <sup>88</sup>	Advanced malignancies with bone metastases	Contraindicated in patients with severe RI (CrCl <30 mL/min). Dose adjustment for patients with mild-to-moderate RI and treatment withheld for renal deterioration. Serum creatinine should be measured before each dose and daily supplementation with calcium 500 mg and vitamin D 400 IU
<b>Antibiotics</b>		
Aminoglycosides (e.g., NA gentamicin <sup>105</sup> and tobramycin <sup>106</sup> )		Dose reductions according to degree of RI. Should be used with caution in patients with existing RI. Serum concentration monitoring of gentamicin recommended adjusting the frequency of dosage according to degree of renal function. Tobramycin should not be used concomitantly with dialysis

**Abbreviations:** CrCl, creatinine clearance; GFR, glomerular filtration rate; IU, international units; NA, not applicable; RI, renal impairment.

not undergo proper monitoring of renal function during treatment with bisphosphonates.<sup>89</sup> A study of physicians treating patients with bone metastases secondary to solid tumors found that managing the risk of RI was their primary safety concern, but there appears to be a discrepancy between clinical recommendations and real-world practice.<sup>90</sup> Treatment with zoledronic acid has been associated with hypocalcemia; some cases have been severe and patients have required hospitalization.<sup>88</sup> Prescribing information recommends that serum calcium should be measured and hypocalcemia should be corrected before initiating therapy with zoledronic acid. Patients treated with bisphosphonates should be adequately supplemented with calcium and vitamin D to minimize the risk of hypocalcemia.<sup>88</sup>

Pamidronate is another bisphosphonate that is associated with nephrotoxicity. Pamidronate is approved at a dose of 90 mg to treat osteolytic bone metastases secondary to breast cancer (2-hour infusion every 3–4 weeks) and osteolytic bone lesions associated with multiple myeloma (4-hour infusion once every 4 weeks).<sup>91</sup> Pamidronate has been associated with nephrotoxic syndrome and focal segmental glomerulosclerosis (FSGS), with multiple cases of FSGS reported in the medical literature.<sup>92</sup> These nephrotoxic effects appear to be dose-dependent and infusion time-dependent.<sup>92</sup> The USA label stipulates that single doses of 90 mg should not be exceeded and serum creatinine should be assessed prior to each treatment. Pamidronate should not be used to treat patients with bone metastases who have severe RI.<sup>91</sup>

Denosumab 120 mg monthly is used for the prevention of skeletal-related events in patients with bone metastases.<sup>93,94</sup> Denosumab is neither excreted through the kidneys nor associated with renal toxicity, so dose adjustment is not required when administered to patients with renal dysfunction.<sup>93,94</sup> However, label recommendations state that all patients who are prescribed denosumab should receive daily vitamin D and calcium supplementation, owing to the risk of developing hypocalcemia.<sup>93,94</sup> This is particularly important for patients with severe RI (CrCl of <30 mL/min) or for individuals receiving dialysis,<sup>87</sup> and in those for whom regular calcium monitoring is required.<sup>93,94</sup> This is in line with the European Society for Medical Oncology clinical practice guidelines for managing bone health in patients with cancer.<sup>58</sup>

### Nephrotoxic antibiotics

Patients with cancer, particularly those undergoing chemotherapy, are at increased risk of developing serious infections that are commonly treated using antibiotics. However, the use of certain antibiotics (or combinations of antibiotics) is associated with acute tubular necrosis owing

to renal excretion, which can result in cumulative kidney damage.<sup>95</sup> Antibiotics associated with acute kidney injury include aminoglycosides, penicillins, cephalosporins and fluoroquinolones. Nephrotoxicity can affect up to 50% of patients receiving these treatments, and the risk of damage increases with advancing age, volume depletion and sepsis. Long treatment courses and high doses of antibiotics can further increase the risk of nephrotoxicity.<sup>95</sup> Therefore, careful dose adjustments may be required to ensure that the balance between nephrotoxicity and efficacy is maintained.

### Dose adjustments or interruptions for optimal patient management

As discussed, many patients will receive nephrotoxic agents as part of their cancer treatment and may subsequently require dose adjustments to manage kidney-related adverse events. In the large USA study of 11,809 patients with bone metastases secondary to solid tumors, 23.4% of patients received a nephrotoxic agent prior to diagnosis of bone metastases, rising to 69% after diagnosis.<sup>32</sup>

Many chemotherapeutic agents are metabolized by the kidney, producing toxic by-products in the process. RI can result in delayed drug excretion and local and systemic toxicity may arise.<sup>96</sup> Chemotherapy dose adjustments are therefore frequently required when administered to patients with RI. In the IRMA study, most (79.9%) patients who were given an anticancer drug received at least one agent that required a dosage adjustment or an agent for which no data were available on use in patients with RI.<sup>24</sup> This affected most patients receiving treatment for prostate cancer (82.9%)<sup>53</sup> or breast cancer (90.4%).<sup>55</sup> For patients with advanced cancers and bone metastases, dose reductions are recommended in those with mild-to-moderate RI receiving intravenous zoledronic acid.<sup>88</sup> In clinical trials, dose adjustments have been reported in approximately one-fifth of patients receiving zoledronic acid.<sup>84,97</sup> Common agents used in cancer therapy that require dose adjustments based on renal function are shown in Table 2.<sup>88,98–107</sup>

### Mitigating renal complications: role of the nephrologist

An important aspect of minimizing the risk of renal injury includes early recognition of RI, or even prevention. This can be accomplished by routine use of eGFR estimation rather than serum creatinine alone (which may be in the normal range in older patients or those with muscle wasting) and urine protein assessment to identify patients with preexisting RI, or close monitoring of urine output to detect acute reductions in renal function. These scenarios may dictate a need to



reduce drug doses, avoid nephrotoxic agents and administer intravenous fluids to correct volume depletion. Perhaps most importantly, early involvement of or routine collaboration with a nephrologist in the care of patients with cancer may improve outcomes.

The nephrologist can assist with proper identification of the presence of preexisting renal disease, or other conditions that put patients at risk of acute kidney injury related to the management of cancer. Acute kidney injury is a common complication among hospitalized patients with cancer and is associated with an increased length of stay and mortality.<sup>108,109</sup> One example in which early intervention by a nephrologist may help is in the case of tumor lysis syndrome, the consequences of which include RI, cardiac arrhythmia and death.<sup>110</sup> Patients at risk of this condition can be identified, enabling the use of prophylactic measures, such as intravenous fluids or xanthine oxidase inhibitors.<sup>111,112</sup> For those with established tumor lysis syndrome, nephrologists can advise on the acceptability of using rasburicase, which helps to clear uric acid from the blood, and in severe cases, of possibly using dialytic therapies.

Another scenario where the assistance of a nephrologist may be beneficial is for the planned administration of potential nephrotoxins, such as intravenous contrast for imaging, certain antibiotics or chemotherapeutic agents.<sup>108</sup> In these cases, collaboration between the nephrologist and oncologist may help achieve the best possible benefit:risk ratio when using these nephrotoxic agents. Nephrologists can advise on the need for dose reductions and ensure the proper maintenance of adequate volume balance, which can reduce the risk of renal injury across the spectrum of nephrotoxic exposures.<sup>96</sup> In addition, nephrologists can identify and recommend the discontinuation of discretionary medications that are potentially nephrotoxic. Nonsteroidal antiinflammatory agents, for example, can in a certain risk context result in renal injury, even after a modest number of doses.<sup>113,114</sup>

Finally, nephrologists can play an important role in the diagnosis of renal disease, particularly for rare conditions that are unique to the cancer context, many of which require renal biopsy for the confirmation of the diagnosis. Examples of these include parenchymal invasion of the kidney by tumor cells (usually observed with leukemias or lymphomas), paraneoplastic glomerulonephritides and thrombotic microangiopathies due to certain chemotherapeutic agents, or the cancer itself.<sup>115</sup>

Given the rapidly evolving field of cancer chemotherapeutics, the prevalence of underlying CKD in elderly patients

with malignancies, and the broadening range of renal complications secondary to cancers or their treatment, there has been increasing recognition of the need for specialized knowledge in this clinical context. This has resulted in the development of a new subspecialty of onconeurology.<sup>116</sup> The American Society of Nephrology has established an Onconeurology Forum Group,<sup>117</sup> and the University of Texas MD Anderson Cancer Center is offering a fellowship training program.<sup>118</sup>

The partnership between nephrologists and oncologists is important for the optimal management of patients; the identification of onconeurology as an independent medical specialty may help enhance this relationship. The development of this specialty and the enhancement of collaboration between experts have the potential for valuable research advances and to encourage guideline preparation on the management of kidney disease in patients with cancer.<sup>119</sup>

## Conclusion

Improvements in cancer therapy mean that patients are surviving for longer periods of time, with a rapidly expanding range of therapeutic options for management of the primary cancer and for its secondary effects such as bone metastases or infections, many of which have the potential for nephrotoxicity. There is, therefore, increasing recognition of the need for attention to kidney disease in the context of cancer. The balance between cancer therapy and preservation of renal function must be considered carefully by physicians treating patients with advanced cancer, with thoughtful choice and dosing of antineoplastic treatments and bone-targeted agents to minimize nephrotoxicity. Collaboration between nephrologists and oncologists may help ensure that care of patients with cancer and kidney disease is optimized.

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