Chapter 2
Chronic Kidney Disease (CKD) in Cancer Patients

Mala Sachdeva, Amit Lahoti and Anna Mathew

List of Abbreviations

ACE	Angiotensin converting enzyme
AKI	Acute kidney injury
ARB	Angiotensin II receptor blocker
CKD	Chronic kidney disease
CIN	Contrast induced nephropathy
ESA	Erythropoietin stimulating agent
ESKD	End-stage kidney disease
FGF	Fibroblast growth factor
GFR	Glomerular filtration rate
HSCT	Hematopoetic stem cell transplantation
NG	Naso-gastric
NJ	Naso-jejunal
PEG	Percutaneous endoscopic gastrostomy
PTH	Parathyroid hormone
VEGF	Vascular endothelial growth factor

M. Sachdeva (✉) · A. Mathew
Division of Kidney Diseases and Hypertension, North Shore University Hospital and Long Island Jewish Medical Center, Hofstra North Shore-LIJ School of Medicine, 100 Community Drive, 2nd Floor, Great Neck, NY 11021, USA
e-mail: msachdeva@nshs.edu

A. Mathew
e-mail: amathew13@nshs.edu

A. Lahoti
Section of Nephrology, Department of Emergency Medicine,
UT MD Anderson Cancer Center, Houston, TX, USA
e-mail: alahoti@mdanderson.org

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Table 2.1 Stages of chronic kidney disease (Adapted from the National Kidney Foundation, Kidney Disease Outcome Quality Initiative (K/DOQI). Clinical practice guidelines for bone metabolism and disease in chronic kidney disease. Am J Kid Dis. 2003;42:S1–201)

Stage	GFR (mL/min/1.73m^2)	Description
1	90+	Normal kidney function but urine or structural abnormalities
2	60–89	Mildly reduced kidney function
3a	45–59	Moderately reduced kidney function
3b	30–44	
4	15–29	Severely reduced kidney function
5	< 15 or on dialysis	Very severe or end-stage kidney failure

Chronic kidney disease (CKD) is defined by a slow and persistent decrease in glomerular filtration rate (GFR) often associated with structural abnormalities of the kidney. Depending on whether there are structural abnormalities or functional decline of kidney function, CKD is classified into different stages (see Table 2.1). CKD is defined as having decreased renal function or structural abnormality for at least a duration of 3 months [1, 2]. The kidney damage is assessed by abnormalities in urinary sediment such as albuminuria or renal imaging, whereas kidney function is assessed by GFR.

In the USA, the prevalence of CKD and end-stage kidney disease (ESKD) is increasing [3]. Studies have shown that older age, diabetes, hypertension, cardiovascular disease, and higher body mass index are associated with CKD [3–5]. The increase in prevalence of CKD is partly explained by the increase in a number of these CKD risk factors.

CKD and cancer are connected in several ways. Not only can cancer—often indirectly, as discussed below—lead to the development of CKD and ESKD but also presence of CKD can be associated with cancer.

Although the overall incidence and prevalence of CKD among cancer patients is still uncertain, there is growing evidence to suggest that the risk is high and still increasing. The extent of risk for developing CKD varies depending on whether the cancer is solid or hematologic in nature, whether patient underwent nephrectomy or hematopoetic stem cell transplantation (HSCT), or whether nephrotoxic chemotherapy was administered.

Case #1

Which of the following patients have an increased risk of developing CKD:

a. A 45-year-old female who is being treated for colon cancer
b. A 75-year-old woman with recent diagnosis of multiple myeloma with cast nephropathy

c. A 50-year-old male who just underwent hematopoeitic cell transplantation for non-Hodgkin's lymphoma
d. All of the above

Solid Malignancies and CKD

In a study of 4864 adult, solid cancer patients having the five most frequently occurring types of cancer (breast, colorectal, lung, ovarian, and prostate), it was reported that 57.4 and 52.9 % of patients had an abnormal creatinine clearance of less than 90 mL/min when calculated with the Cockcroft–Gault formula and the modification of diet in renal disease (MDRD) formula, respectively [6]. Similarly, in a more recent study of 1218 adult, solid cancer patients receiving chemotherapy, 64.0 % were found to have a decreased GFR of less than 90 mL/min/1.73 m^2. Since different cancer types behave differently and their treatments are different, all cancer patients, regardless of the type of cancer, were found to have increased risk of renal insufficiency [7]. Both studies suggest that the frequency of renal insufficiency is routinely underestimated when the physician bases their judgment on the serum creatinine alone. Thus, renal function must be estimated with formulas which take into account gender, age, and weight of an individual [6, 7]. In addition, both studies excluded those with multiple myeloma and hematologic malignancies. Had these populations been included, the burden of CKD would evidently have been higher.

Multiple Myeloma and CKD

In patients with multiple myeloma, impaired renal function is present in more than 20–30 % of the population at the time of diagnosis [8, 9]. At some point in their disease course, approximately 50 % of them may develop acute kidney injury (AKI) or CKD [9]. Renal failure was more prevalent in those who had more severe hypercalcemia, anemia, and Bence Jones proteinuria [9]. Reversibility of renal failure depended on serum creatinine levels, presence of hypercalcemia, and the extent of proteinuria [8]. Survival was significantly less in those who had renal failure as compared to those with normal renal function, with median survival ranging from 4 months to 1 year, as shown in another study [8].

HSCT and CKD

HSCT is performed more frequently for various hematologic malignancies. CKD following HSCT has been shown to be relatively common and occurring in approximately 16.6–23 % of HSCT patients [10–12]. Some literature suggests higher rates

depending on definition of CKD. Risk factors for CKD in this population included: AKI, total body irradiation, graft versus host disease, and long-term calcineurin inhibitor use [10].

Case #1 Follow Up and Discussion
The correct answer is choice d. As discussed above, solid malignancies, multiple myeloma, and HSCT have all been associated with development of CKD.

CKD and Cancer Development

Case #2
A 71-year-old female is on hemodialysis for the past 4 years. Which of the following cancer is she at most increased risk of developing?
a. Lung cancer
b. Breast cancer
c. Kidney cancer
d. Colon cancer

Studies over the past 30 years have suggested an increased risk of developing cancer in patients with ESKD. Population based studies have also shown an association of mild to moderate CKD and an increased risk of cancer. Potential reasons for this increased risk include the presence of chronic urinary tract infections, a weakened immune system, prior treatment with cytotoxic or immunosuppressant drugs, nutritional deficiencies, and impaired DNA repair mechanisms. Other risks include the environmental exposures leading to cancer and renal failure or acquired cystic renal disease [13, 14].

Cancer rates are higher in patients with ESKD on hemodialysis compared to the general population. In a retrospective analysis of over 800,000 patients on dialysis over an average follow up of 2.5 years, the standardized incidence ratio of cancer was 1.18. Kidney, bladder, thyroid, and Kaposi's sarcoma had the highest risks. Patients on dialysis have increased risk of lower urinary tract disease and are more susceptible to viral carcinogenesis (e.g., hepatitis B and C). The risk of kidney cancer increases with increased time on dialysis. This seems to be secondary to acquired cystic renal disease associated carcinoma. Other risk factors for cancer include dialysis-induced immune dysfunction, prolonged analgesic abuse, and carcinogenesis from prior immunosuppressive or cytotoxic therapy. ESKD after stem cell transplant is associated with increased mortality compared to ESKD from other causes. The cancer risk after

starting dialysis has been shown to increase from 10 to 80 %. [15, 16]. Of a cohort of 831,804 patients on dialysis in the USA, Europe, Australia, and New Zealand, 3 % developed cancer after 2.5 years of follow up [14]. There was a higher risk of cancer in patients younger than 35 [14]. In addition, there was a high risk of kidney, bladder, thyroid, and other endocrine organs [14]. Activation and exposure to viruses such as hepatitis B and C, Epstein–Barr virus, and human papillomavirus likely accounted for the increased risk of other types of cancer. Contrary to bladder cancer, the risk of kidney cancer increased with time on dialysis. Acquired renal cystic disease on dialysis may contribute to this risk. There was difference in risk for cancer between hemodialysis and peritoneal dialysis. Higher rate of cancer was detected in Australia and New Zealand versus Europe and the USA. However, this may be the result of ascertainment bias given the under reporting of cancer in the latter. In another analysis from three large dialysis registries in the USA, Europe, and Australia, cancers of the kidney and bladder were more common, and there was increased risk relatively in the younger population and the female patients [13]. In a study of 28,855 patients who were on dialysis, there was a fourfold increase in ESKD related cancers, namely kidney, urinary tract, and thyroid cancers and a smaller yet still increased risk of cancers, 20 related to immune deficiency [16]. For all cancers, the risk was higher in the individuals less than 50 years old [16].

Studies on the CKD population have been conducted to determine the association of CKD and cancer risk in the older population. One such study from Australia demonstrated that men with CKD had an increased risk for cancer. This risk for men began at an eGFR of 55 ml/min/1.73 m^2, and posed a greatest risk when eGFR was less than 40 ml/min/1.73 m^2. Men with CKD were more at risk for lung and urinary tract cancers [17]. In a more recent analysis, eGFR < 60 mL/min/1.73 m^2 appears to be a significant risk factor for death from cancer [18]. The excess cancer mortality in those with reduced kidney function varied with site, with the greatest risk in those with breast and urinary tract cancer [18]. Each decrease in eGFR by 10 ml/min/1.73 m^2 increased the risk of cancer by 29 % in men. Lung and urinary tract cancers comprised most of the excess cancer risk. Residual confounding (e.g., occupational exposures) was speculated to explain the lack of increased cancer risk in women with CKD. [18]

CKD is also a significant risk factor for both cardiovascular and non-cardiovascular mortality in patients with cancer. Fried et al. were one of the first to show an increase in cancer mortality in patients with decreased renal function [19]. Among 4637 patients in the Cardiovascular Health Study, patients with cystatin C levels in the fourth quartile versus the first quartile had a 79 % increase in cancer mortality rate. The IRMA study was a French observational study that included 4684 patients with cancer, of which 53 % had a eGFR less than 90 ml/min/1.73 m^2 and 12 % had an eGFR less than 60 ml/min/1.73 m^2 [20]. Patients with CKD stage 3 or lower had a 27 % higher mortality. Over one half of these patients required a dose adjustment of chemotherapy, reflecting a practical impact of CKD on this population. In another study of 8223 patients in Korea, CKD was an independent predictor of cancer-specific mortality, which remained significant in a multivariate model [21]. Iff et al. studied 4077 patients in the Blue Moutains Eye Study and found an 18 % increase in mortality for every 10 ml/min/1.73 m^2 reduction in eGFR [18]. Breast

and urinary tract cancers conferred the greatest risk of mortality among patients with CKD. The largest study to date included a cohort of 123,717 patients with a median follow up of 7 years [22]. Patients with CKD had a 20 % increase in cancer mortality compared to patients with normal renal function. Baseline CKD was associated with an increased risk of hepatic, renal, and urinary tract malignancies. Poor nutrition, increased oxidative stress, proinflammatory state, and procoagulant state were proposed as mechanisms for the increased cancer risk in these patients.

Proteinuria is also associated with the development of cancer. In a 10 year follow up of 5425 patients without diabetes or macroalbuminuria, each standard deviation of albuminuria (log of albumin to creatinine ratio) was associated with a 20 % increased risk cancer [23]. Patients with the highest quintile of albumin-to-creatinine ratio compared to the lowest quintile had a relative risk of 8.3 and 2.4 for the development of bladder and lung cancer, respectively.

Case # 2 Follow Up and Discussion
The correct answer is choice c. While dialysis patients are at increased risk for all malignancy, the highest risk is cancer of the urinary tract. Kidney and bladder malignancies are the most common.

Screening for CKD in Cancer Patients

Case #3
A 70-year-old Caucasian female with a history of membranous nephropathy diagnosed 3 years ago was diagnosed with colon cancer shortly thereafter. She was treated with surgical resection and adjuvant oxaliplatin-based chemotherapy for colon cancer and is now in remission. On routine laboratory tests she is found to have a serum creatinine of 1.5 mg/dL. She is 160 cm tall and weighs 65 kg. Urine studies from 3 years ago revealed 5 g of proteinuria and laboratory studies at that time revealed a creatinine of 1.0 mg/dL. One year ago her creatinine was 1.2 mg/dL. At that time, her urinalysis was not significant for proteinuria or microscopic hematuria. Which of the following is correct?

a. The patient has AKI
b. The patient has CKD stage 1
c. The patient has CKD stage 2
d. The patient has CKD stage 3
e. The patient has CKD stage 4

In the general population, there is some controversy as to whether routine screening for CKD by blood work and/or urine testing is cost-effective. However, it should be a priority to define and grade CKD in cancer patients, by checking a serum creatinine

Table 2.2 GFR estimating equations

Cockcroft Gault (in mL/min)	$\frac{(140-\text{age})\times\text{weight}}{72\times\text{SCr}} \times (0.85 \text{ if female})$
MDRD (in mL/min/1.73 m^2)	$185 \times (\text{SCr})^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if African American})$
Jelliffe (in mL/min)	$\{[98 - 0.8 \times (\text{age}-20)] \times [1 - (0.01 \times \text{sex})] \times (\text{BSA}/1.73)\}/(\text{SCr} \times 0.0113);$
Wright (in mL/min)	$\{[6580 - (38.8 \times \text{age})] \times \text{BSA} \times [1 - (0.168 \times \text{sex})]\}/\text{SCr}$

SCr Serum Creatinine in mg/dL
Sex: Male = 0; Female = 1
BSA Body surface area (DuBois)
Age: in years
Weight: in kilograms

and estimating GFR. Since kidney plays a pivotal role in drug elimination, having a good estimate of kidney function is essential for proper drug dosing especially that of many chemotherapeutic agents.

Case #3 Follow Up and Discussion
The correct answer is choice d. For the patient in this question, it is likely that she has CKD given that her creatinine has been elevated for more than a 3 month period. Her history of membranous nephropathy could be a potential contributing factor. While cisplatin has been associated with tubular toxicity, there have been no reports of oxaliplatin-induced nephrotoxicity [24]. After estimating her GFR, she is found to be at stage 3 CKD with an estimated creatinine clearance of 35 mL/min using the Cockcroft–Gault equation.

In addition, as stated earlier, CKD is an independent risk factor for cardiovascular disease, progression to ESKD, and all cause mortality [25–28]. This in itself can be helpful at preventative behaviors.

GFR can be measured directly by measuring renal excretion of radioisotopes or by nuclear renogram. Whereas these measures are highly accurate and directly measure GFR, they are expensive and not often readily available. A more common method to ascertain kidney function is by estimating the GFR through one of several available estimating equations. These equations use readily available variables such as serum creatinine, age, gender, weight, and race and are listed in Table 2.2.

The Cockcroft–Gault is the most commonly used equation and the modified Jelliffe formula is used in several oncology trials for the purpose of estimating GFR. Recently, the MDRD equation has gained popularity, but was derived in a healthy population, and is currently not recommended for use in the oncology patient. Based on recent literature comparing various GFR-estimating equations in oncology patients, it is currently recommended to use the Cockcroft–Gault equation [29]. If the GFR is greater than equal to 50 ml/min and the patient is greater than 70 years and/or

BMI greater than equal to 30, the Wright formula gives the best estimate of GFR [24] (See Table 2.2).

Microalbuminuria is defined at 30–300 mg/day of urine albumin and thus is not detected by a urine dipstick test alone. Urine protein is comprised of albumin and Tamm—Horsfall proteins. In certain hematological malignancies, light chains are also excreted in the urine, called Bence Jones proteins. This abnormal proteinuria is not detected by urine dipstick test.

Checking urine for microalbumin is a simple and important tool to detect individuals with early or undiagnosed CKD. When microalbuminuria is present, GFR is typically elevated, normal, or slightly impaired [30]. Microalbuminuria is defined as 30–300 mg/day of urine albumin, and macroalbuminuria is defined as greater than 300 mg/day of urine albumin. Following are the ways to check for microalbuminuria/proteinuria: (1) urine albumin-to-creatinine ratio (ACR), (2) urine protein-to-creatinine ratio (PCR), (3) reagent strip urinalysis for total protein with automated reading, and (4) reagent strip urinalysis for total protein with manual reading. In all of the above, an early morning urine sample is preferred, and the test should always be confirmed [2].

Albuminuria is not only important for detecting CKD, but its significance in long-term prognosis bears relevance. It is associated with increased all-cause and cardiovascular mortality, as well as progression to end-stage renal disease. These risks exist even in the absence of a reduced GFR [31].

Management of the Cancer Patient with CKD

Drug Dosing and Polypharmacy

Abnormal renal function serves as a risk factor for drug induced nephrotoxicity. In patients with CKD, drug pharmacokinetics may be altered. For example, some drugs that are dependent on protein binding may end up in higher than normal concentrations due to hypoalbuminemic states. Other drugs may have altered renal excretion due to the reduction in GFR [20]. Approximately half of all anticancer drugs are excreted in the urine as active metabolite or unchanged drug. Due to decreased clearance issues, these drugs need adjustment to avoid accumulation of toxic metabolites or overdosage of the medication [6]. In the CKD population, choosing the non-nephrotoxic or less nephrotoxic drug would be ideal. However, in cancer patients requiring chemotherapy, the therapeutic options are often limited. For this reason, drug-induced nephrotoxicity should be noted, discussed, and appropriately monitored and managed according to the medication guidelines.

Another important factor is drug–drug interactions. A careful review of medications is important to avoid the risk of combining anticancer and non-anticancer medications interactions [7]. For example, NSAIDs and ACE inhibitors may potentiate nephrotoxicity especially in a volume-depleted individual.

Finally, the potential of further deterioration of renal function with chemotherapy, which would then precipitate ESKD, must be considered [6]. In this situation, timely referral to a nephrologist would be ideal to allow for timely discussions with the patient regarding options of either renal replacement therapy or end of life issues.

Hypertension

Case #4
You are seeing a 55-year-old white female with a creatinine of 1.5 mg/dL in your office. She has recently been diagnosed with breast cancer and is awaiting assessment by surgical oncology. She is a current smoker. Her blood pressure has been 160/95 and 155/90 mmHg when checked last 2 times in your office. Her albumin to creatinine ratio in the urine is 50 mg/g, and her serum potassium is 5.2 mEq/L. What is the best initial intervention?

a. Life style interventions including daily exercise, DASH diet, and smoking cessation
b. Initiation of an angiotensin converting enzyme (ACE) inhibitor
c. Initiation of an ACE inhibitor and a thiazide-type diuretic
d. a and b
e. a and c

Hypertension is one of the most common comorbidities encountered with malignancy. Preexisting hypertension, as well as hypertension due to certain chemotherapy agents, account for the majority of those with hypertension [32–34] (See Table 2.3). In addition to these medications, surgery or radiation therapy involving the head and neck can be associated with hypertension. The mechanism of this is thought to be baroreflex failure, causing either labile hypertension or hypertensive crisis. Managing hypertension is important in this patient population to reduce long-term adverse consequences and decrease progression of CKD [32].

Case #4 Follow Up and Discussion
The correct answer is choice e. Life style interventions and initiation of an ACE inhibitor and thiazide-type diuretic. According to the most recent JNC VIII guidelines for hypertension management [32], patients with CKD of all ages and all races should have a goal blood pressure of less than 140/90 mmHg. Lifestyle interventions should be implemented throughout the course of treatment. While initial choice of medication should be individualized, an ACE inhibitor or an angiotensin receptor blocker (ARB) should be considered as first line of therapy, especially in the case of microalbuminuria. In this case,

Table 2.3 Chemotherapy-induced hypertension

Medication	Class	Reason for hypertension
Tamoxifen	Estrogen receptor binder	Via estrogenic effects
Cyclosporine	Calcineurin inhibitor	Endothelial dysfunction, arterial vasoconstriction and activation of the renin–angiotensin system
Cisplatin	Alkalating agents	Possible drug induced renovascular mechanisms
Dexamethasone, prednisone	Steroids	Salt and fluid retention
Bevacizumab	Vascular endothelial growth factor (VEGF) monoclonal antibody	Inhibition of VEGF signaling pathway leading to suppression of nitric oxide synthase, resulting in decreased nitric oxide production and reduced prostacyclin activity in the endothelium
Sorafenib, sunitinib, pazopanib, vandetanib, axitinib, regorafenib, cabozantinib	Small molecule tyrosine kinase inhibitor	Inhibition of VEGF signaling, as above
Aflibercept	Recombinant fusion protein which prevent VEGF receptor binding/activation to their receptors	Inhibition of VEGF signaling, as above

a thiazide-type diuretic should also be employed to help control both blood pressure and serum potassium. In the African American population, the first line treatment may be a calcium channel blocker or thiazide-type diuretic.

Initial approach to hypertension would be lifestyle modifications such as weight loss, increased physical activity, DASH diet, and moderate alcohol consumption. Pharmacologic therapy should be instituted if blood pressure remains high.

According to the most recent JNC VIII guidelines, goal blood pressure for those who are 60 years or older should be less than 150/90 mmHg. A target blood pressure of less than 140/90 mmHg is recommended in all other age groups and in hypertensive patients with diabetic or non-diabetic CKD [32]. The choice of which antihypertensive agent should be used depends on the patient's comorbidities and ethnicity. In the nonblack population, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic, calcium channel blocker, ACE inhibitor, or ARB. In the black population, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic or calcium channel blocker. Patients with CKD and hypertension should be started on ACE inhibitor or ARB.

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