Chronic Kidney Disease and Cancer

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Before You Start: Facts You Need to Know

- Chronic kidney disease (CKD) is highly prevalent in cancer patients.
- Cancer prevalence is higher in the CKD population, for a number of tumors but especially cancers of the urogenital tract.
- Cancer screening in the CKD population is key, but appropriate screening tools and protocols remain to be defined.
- Measuring the actual glomerular filtration rate (GFR) of a patient (isotopic methods) is the gold standard method but cannot be routinely performed.
- Estimating the GFR by calculations from serum creatinine can be performed and the most recent CKD-EPI formula should be utilized in determining dose adjustments for chemotherapeutic agents.
- Nephrotoxic drugs should be avoided, whenever possible, in patients presenting with preexisting renal impairment.
- The role of both underlying cancer and anticancer therapies in leading to CKD is important to recognize as the preservation of GFR is likely to improve outcomes.

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33.1 Introduction

The overall incidence of cancer is rising throughout the world. In addition, as populations age and the prevalence of conditions such as diabetes and hypertension increases, the prevalence of chronic kidney disease (CKD) is also increasing. Very few studies have looked at the incidence and prevalence of CKD among cancer patients. One study evaluated the causes of CKD in patients who had a diagnosis of cancer in their childhood. Over 700 childhood cancer survivors were followed and their kidney function was assessed longitudinally [1]. The factors that were major predictors of loss of glomerular filtration rate (GFR) later in life after experiencing treatment for childhood cancers were: nephrectomy, abdominal radiation, high dose ifosfamide exposure, and high dose cisplatin exposure. CKD following cancer can be a result of numerous etiologies, several of which may be acute but have lasting deleterious effects to lower GFR and lead to progressive loss of nephrons. These include: acute tubular necrosis (ATN) (either due to nephrotoxins or in the setting of ischemia (sepsis)), tumor infiltration of the renal parenchyma, and/or vascular, tubular, interstitial, or glomerular toxicities of chemotherapy agents. The toxicities from chemotherapy are the most common causes of CKD in cancer patients. In addition, since many of these patients are living longer, they are not immune from developing CKD asso-

M. Arıcı (ed.), *Management of Chronic Kidney Disease*,
https://doi.org/10.1007/978-3-031-42045-0_33

ciated with common causes such as hypertension and diabetes mellitus.

What is striking is that CKD, especially end-stage kidney disease (ESKD), has a significant impact on cancer therapy and outcomes. The CANcer and DialYsis (CANDY) study [2], which retrospectively evaluated treatment patterns and clinical outcomes in patients undergoing chronic dialysis who subsequently developed cancer, showed that chemotherapy was omitted or prematurely stopped in many cases or was often not adequately prescribed, and survival was poor in this cohort of patients. This study highlights the challenges oncologists face when treating patients with cancer on chronic dialysis. Unfortunately, no such study exists for CKD patients. While one French study demonstrated that few patients in their centers required dose adjustments for chemotherapy agents due to a prior diagnosis of CKD [3], another analysis of patients from Belgium did note that the prevalence of patients with cancer and estimated GFR < 90 ml/min per 1.73 m^2 was 64% [4]. These are important findings suggesting that GFR needs to be carefully assessed in patients with cancer. Furthermore, for many chemotherapeutic protocols, dose adjustments for suboptimal GFR are poorly defined and not evidence-based.

The risk of cancer in CKD patients is higher than the general population for certain tumor types such as renal cell carcinoma [5, 6]. Wong et al. analyzed a cohort of over 3000 patients over a mean of 10 years. They found that men, and stage 3 or higher CKD had an increased risk of cancer. The risk increased with GFRs starting at 55 ml/min per 1.73 m^2 and with an increase in risk of 29% for every 10 ml/min decrement [5]. The major cancers involved were primarily of urinary origin and lung cancers. Weng et al. [7] published the largest study to date analyzing the cancer-specific mortality in CKD. In this study, CKD was significantly associated with liver cancer, kidney cancer, and urinary tract cancers. In kidney and urological cancers, the lower the GFR, the higher the mortality risk from kidney and urological cancers. In addition, CKD appears to be a risk factor for poorer outcomes with cancer. While not clear, an underlying pro-inflammatory state, altered host immunity, and nutritional status might be major contributors to this association. Furthermore, alterations in potentially curative therapeutic regimens may occur in the setting in CKD which may limit efficacy.

33.2 Assessment of GFR in Cancer Patients

Chemotherapeutic agents used to treat cancer generally have narrow therapeutic indices along with potentially serious adverse toxicities. Accurate dosing is required to ensure optimal outcomes and to avoid toxicity. For those drugs excreted through the kidney, a precise understanding of kidney function is needed to ensure achievement of therapeutic levels and avoidance of these toxicities. Unfortunately, many drugs used for the treatment of cancer lack data on appropriate dosing when kidney function is impaired. This is not acceptable as it places the large number of patients with chronic kidney disease at risk for both toxicities and suboptimal outcomes.

In general, two pathways are involved in the excretion of drugs and their metabolites by the kidney: glomerular filtration and tubular secretion. Glomerular filtration is relevant for smaller, non-protein bound substances. Tubular secretion is a more common pathway for protein-bound compounds. In addition, tubular reabsorption of a drug can also occur which can raise the concentration of the drug. In most cases, the best measure of kidney function is the glomerular filtration rate (GFR) which has generally been accepted as a measure of functioning kidney mass [8]. Measures to directly and indirectly measure GFR have been well validated and there is extensive experience with their operational characteristics which makes their use ideal in design of clinical trials, determination of appropriate dosing guidelines for various levels of kidney function, and for the care of patients with cancer. In addition, a critical and often underappreciated issue is that he United States Food and Drug Administration

(FDA) has recommended that pharmacokinetic studies in kidney impairment models be conducted for medications which are not eliminated by the kidney, recognizing the fact that non-kidney clearance mechanisms can be altered in patients with impaired kidney function [9].

While many methodologies exist to measure GFR, many are not practical in daily clinical use [10]. Serum markers (such as creatinine and cystatin C) have been developed to be used in GFR estimating equations, while in some circumstances, more precise determination of GFR is needed and then urinary clearance of an ideal filtration marker can be utilized (typically through radionuclides and radiocontrast agents where clearance can be determined as the amount of indicator injected divided by the integrated area of plasma concentration curve over time) [11, 12]. Substances such as ^{125}I-iothalamate and ^{51}Cr-ethylenediaminetetra-acetic acid (EDTA) (detected by plasma levels) or 99m-Tc mercaptoacetyltriglycine (MAG3) and 99m-Tcdiethyl triamine penta-acetic acid (99mTc-DTPA) (detected by gamma counter) can be used for direct GFR measurement [11, 12]. More typical and more practical is estimation of GFR through various regression equations that may include: creatinine clearance estimation, estimated GFR measurements, or cancer-specific equations that aim to take into consideration patient-specific factors impacting kidney function measurement. While the National Comprehensive Cancer Network (NCCN) and the International Society of Geriatric Oncology (SIOG) recommend an assessment of kidney function before the administration chemotherapeutic drugs, even in patients with "normal" kidney function, there are no collective guidelines declaring which method of estimating kidney function is preferred in patients with cancer [13].

The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was developed to improve shortcomings of prior equations and is most commonly used in current clinical practice [14]. This equation utilizes serum creatinine values as well as age, gender, and race to calculate an estimated GFR [14]. There are also forms of the CKD-EPI equation that incorporate serum cystatin C to better refine GFR estimation [15]. Data suggests that 3.6% of US adults would be classified as having CKD solely on the basis of a creatinine-based GFR estimate of 45–59 ml per minute per 1.73 m^2 [16]. A strategy of measuring cystatin C when the creatinine-based estimate is in this range and then re-estimating GFR with the use of both these markers could correctly reclassify a substantial proportion of such patients as not having chronic kidney disease and not being at high risk [15, 17]. The CKD-EPI equation is currently recommended by the National Kidney Foundation-Kidney Disease Outcome Quality Initiative (NKF-KDOQI) and the Kidney Disease Improving Global Outcomes guideline groups [18]. A point of recent controversy is that the CKD-EPI equation incorporates race (black vs. non-black) as a variable and the appropriateness of this has been questioned as race is a social and not a biological construct [19]. Thus, it may be appropriate to avoid race correction in the estimation of GFR but more study is needed [20]. Over the past several years, several publications have shown superior performance of the CKD–EPI equation in the cancer patient population over other methodologies [13].

A major caveat with the use of the CKD-EPI equation is that cancer patients who are ill may be in a non-steady-state condition where estimating equations are less likely to be accurate. These changes in GFR over time were demonstrated in a large retrospective evaluation of patients with solid tumors without CKD. Patients had an average decline in GFR of 7 mL/min/1.73 m^2 after 2 years of diagnosis or a CKD stage decline from stage 2 to 3 or 4 [21]. In another study, the risk of acute kidney injury was 17.5% and 27% in the first and fifth year of cancer diagnosis, respectively, demonstrating that GFR is changing in a substantial number of cancer patients [22]. In these circumstances, the use of GFR estimating equations may give false values. This issue highlights the need for direct, real-time measurements of GFR at the point-of-care. This ability would allow for adjustment of drug dosing based upon accurate assessment of measured GFR. There are now two methodologies in development that allow for direct quanti-

tative GFR measurement that may simplify acquisition of this critical data. One technique uses a novel 5-kilodalton fluorescein carboxymethylated dextran (rapidly filtered by the kidney) and the other uses a transdermal sensor to measure the removal of a fluorescent tracer from the blood [23–25]. Both of these methods would allow for a new paradigm of care where patients might be expected to get measured GFR levels just prior to drug dosing. The measured GFR would be used to adjust the dose of chemotherapy to ensure maximal efficacy and minimal toxicity. In addition, these techniques could be used during drug development to develop more precise dosing guidelines.

33.3 Etiologies of CKD in Cancer Patients

There are numerous unique etiologies of CKD in patients with underlying cancer. The most common include CKD due to chemotherapeutic agents, glomerular disorders, renal cell cancer, paraprotein-induced kidney disease and associated with stem cell transplantation.

33.3.1 Chemotherapy and Targeted Therapy Induced CKD

Many chemotherapeutic agents are associated with nephrotoxicity. Risk factors that can increase nephrotoxicity include patient age, preexisting CKD, exposure to other nephrotoxins (such as aminoglycoside antibiotics and iodinated contrast agents), and volume depletion. Most commonly, chemotherapy agents lead to electrolyte disorders or AKI, but there is significant risk of CKD from some agents. Table 33.1 lists some of the more common renal toxicities of chemotherapy agents [26].

Cisplatin is a potent tubular toxin, associated with many tubulopathies [27, 28]. These changes are mild and transient in most patients and sustained elevations in serum creatinine are less common. In one study of 54 patients followed for more than 3 months, only one developed late onset azotemia [29]. Although long-term follow-up studies indicate that kidney function either remains stable or improves over time, some patients may have a significant reduction in creatinine clearance despite normal serum creatinine levels [30].

Table 33.1 Chemotherapy, targeted therapy, and immunotherapy associated kidney dysfunction

Compartment of the kidney	Toxicity	Chemotherapy agent
Glomerular	Membranoproliferative glomerulonephritis	Gemcitabine, sirolimus
	Minimal change disease	Interferon alpha, beta, and gamma, pamidronate, doxorubicin (adriamycin), daunorubicin (daunomycin), sirolimus, nivolumab
	Focal segmental glomerulosclerosis	Sirolimus, temsirolimus, everolimus, doxorubicin (adriamycin), daunorubicin (daunomycin)
	Collapsing glomerulopathy	Interferon alpha, beta, and gamma, pamidronate, gefitinib, sirolimus, doxorubicin (adriamycin), daunorubicin (daunomycin), clofarabine
	Membranous nephropathy	Sirolimus
	Lupus like nephritis	Ipilimumab
	IgA nephropathy	Sirolimus
Vascular	Thrombotic microangiopathy	Anti-angiogenic agents (bevacizumab and tyrosine kinase inhibitors), gemcitabine, cisplatin, mitomycin and interferons, pembrolizumab, and nivolumab
Tubular/interstitial	Acute tubular necrosis	Platinums, zoledronate, ifosfamide, mithramycin, pentostatin, imatinib, diaziquone, pemetrexed, clofarabine, arsenic trioxide
	Acute interstitial nephritis	Sorafenib, sunitinib (but can be any chemotherapy)
		Checkpoint inhibitors (ipilimumab, pembrolizumab, nivolumab)
	Crystal nephropathy	Methotrexate

Alkylating agents such as ifosfamide, cyclophosphamide, and melphalan are used for many cancer treatments. Of these, ifosfamide is most often associated with nephrotoxicity [31]. Moderate to severe renal injury occurs when doses are above 100 g/m^2. In addition, ifosfamide may lead to long-term reductions in GFR. Farry et al. published long-term follow-up of adult patients at a single center that received ifosfamide and they found that there was a 15 ml/min decrease in GFR in the first year of treatment and then 22 ml/min in the next 4 years after treatment [32].

Nitrosoureas have been noted to cause CKD. Semustine, carmustine, and lomustine are lipid soluble alkylating agents used in treatment of brain tumors [33, 34]. All three of these agents produce dose-related nephrotoxicity which can progress to CKD. In one study of over 150 patients treated with semustine and/or carmustine, all patients who received more than ten doses developed CKD [34]. Typically in these cases the urinary sediment is bland with not much proteinuria. In many patients, the serum creatinine may not rise till months after treatment. Biopsy findings show extensive glomerular and interstitial fibrosis and tubular atrophy [33].

Targeted therapies have recently evolved as promising agents for treatment of various cancers. Tyrosine kinase inhibitors and vascular endothelial growth factor inhibitors are some examples of such therapies. Tyrosine kinase inhibitors are classically associated with thrombotic microangiopathy (TMA). One case series reported that over time there is a chronic interstitial insult that leads to CKD in patients receiving these drugs [35]. Both sunitinib and sorafenib have been associated with acute interstitial damage and ultimately in chronic interstitial damage [35]. In addition, alectinib, a second generation anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitor, has been reported to be rarely associated with progressive CKD [36].

Many antiangiogenic agents and tyrosine kinase inhibitors lead to renal limited or systemic TMA and/or hypertension [37, 38]. Renal limited TMA may go undiagnosed and requires a high degree of clinical suspicion for confirmation by kidney biopsy. However, if diagnosed early, the syndrome can be reversible in some cases with cessation of the offending agent. Unfortunately, development of CKD is not unusual in patients with this syndrome [39].

In addition, all glomerular toxicities of chemotherapy agents can be potential causes of CKD if the insult is ongoing and long-term. Thus, for all agents with any potential nephrotoxicity, monitoring of GFR and urine studies should be mandatory. Early diagnosis and rapid cessation of offending medications is critical to limit renal fibrosis and the eventual development of CKD.

Newer immunotherapy includes checkpoints inhibitors such as anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and anti-programmed death 1 (PD-1) [40]. These agents have revolutionized the treatment of malignancies by engaging the patient's own immune system against the tumor rather than targeting the cancer directly. Drugs of this class include: ipilimumab, pembrolizumab, and nivolumab. These drugs have been associated with acute kidney injury that is generally immune-mediated and consistent with acute interstitial nephritis [41]. The onset of kidney injury seen with PD-1 inhibitors is usually late (3–10 months) compared to CTLA-4 antagonists related renal injury, which happens earlier (2–3 months) [41]. Glomerular diseases such as minimal change disease, membranous nephropathy, TMA, and lupus like nephritis also have been rarely reported with these agents. PD-1 as opposed to CTLA-4 inhibitors has been associated with kidney rejection in transplantation [41]. Steroids appear to be effective in treating the immune-related adverse effects noted with these agents [41]. Whether these drugs are associated with CKD is not yet clear but vigilance in monitoring GFR over time is warranted.

33.3.2 Paraneoplastic Glomerular Disease and CKD

Various kinds of cancers have been associated with glomerular diseases which can lead to progressive CKD. The pathophysiology underlying

this association in most cases is not clear. Both solid and hematological malignancies can produce abnormal tumor cell products which could lead to paraneoplastic glomerular disease. Table 33.2 summarizes the major solid and hematologic malignancies that have been associated with glomerular diseases.

Table 33.2 Solid and hematologic malignancies associated with different glomerular diseases

Malignancy	Glomerular diseases reported
Lung cancer[a]	MN, MCD, MPGN, IgAN, FSGS, CGN, TMA
Colon cancer	MN, MCD, CGN
Stomach cancer	MN
Pancreas cancer	MN, MCD, IgAN
Bladder cancer	MCD
Renal cell cancer	AAA, CGN, IgAN, MCD,FSGS, MPGN
Prostate cancer	MN, CGN
Breast cancer	MN, FSGS, MPGN,TMA
Esophageal cancer	MPGN, FSGS
Gastric cancer	MPGN, CGN, TMA
Head and neck cancer	MN, IgAN
Ovarian cancer	MN,MCD
Cervical cancer	MN
Endometrial cancer	MN
Melanoma	MN, MPGN
Skin cancers (basal, squamous cell)	MN
Hodgkin's disease	MCD, MN, MPGN, IgAN, FSGS,CGN, AAA,Anti GBM
Non-Hodgkin's disease	MN, MCD, MPGN, IgAN, FSGS
Chronic lymphocytic leukemia	MN, MCD, MPGN, FSGS, CGN
Acute myelogenous leukemia	MN, FSGS
Chronic myelogenous leukemia	MN, MCD, MPGN
Monoclonal gammopathy of unclear significance	MPGN
T cell leukemia	FSGS

MN membranous nephropathy, *MCD* minimal change disease, *MPGN* membranoproliferative glomerular nephritis, *FSGS* focal segmental global sclerosis, *CGN* crescentic glomerulonephritis, *IgAN* IgA nephropathy, *TMA* thrombotic microangiopathy, *AAA* AA amyloidosis, *GBM* glomerular basement membrane

[a]Includes small cell, nonsmall cell, squamous cell, and bronchogenic cancers

Membranous nephropathy (MN) is the most commonly reported glomerular disease in patients with solid tumors [42, 43]. The prevalence of malignancy in 240 patients with biopsy proven MN was around 10% [44]. Interestingly, only half of these patients had cancer-related symptoms at the time of their biopsy. Most were diagnosed with cancer within a year of being diagnosed with MN [44]. The finding of nephrotic-range proteinuria in a patient with cancer or the development of proteinuria within a few months of diagnosis of cancer should raise strong suspicion of glomerular disease, especially MN.

Delineating primary from secondary/cancer-associated MN has been a great challenge for nephrologists and pathologists. Various studies have evaluated different parameters which could help make this differentiation. These parameters could be clinical or historical clues, serological markers, or histopathological findings on the kidney biopsy.

Podocyte transmembrane glycoprotein M-type phospholipase A2 receptor (PLA2R) autoantibodies were first identified by Beck et al. in 2009 [45]. It was postulated that these circulating antibodies were mainly found in patients with primary MN. A study analyzed 10 patients with solid tumors and MN and three out of these 10 patients had both elevated levels of anti-PLAR2R antibodies and moderate glomerular IgG4 deposition on kidney biopsy; findings suggestive of an underlying primary MN in these patients with solid tumors [46]. These three patients had persistence or relapse of proteinuria despite tumor resection, further supporting the notion that these were indeed patients with primary MN. Hoxha et al. showed enhanced staining of PLA2R in glomeruli of patients with primary MN compared with normal staining in tumor-associated MN [47]. Ohani et al. showed increased glomerular deposition of both IgG1 and IgG2 subtypes in patients with cancer-associated MN as compared with primary MN [48]. While the presence of circulating anti-PLA2R antibodies or enhanced glomerular PLAR2R staining or the predominance of IgG4 in the glomeruli of patients with MN suggests primary MN even in the presence of

cancer, caution is warranted in excluding malignancy solely on the basis of anti-PLA2R antibodies. A recent study by Radice and colleagues analyzed 252 consecutive MN patients and found that 7 patients with cancer were anti-PLA2R positive [49]. Thus, anti-PLA2R positivity in a patient with MN should not be considered sufficient to abstain from seeking a secondary cause, especially in patients with risk factors for neoplasia.

Minimal change disease (MCD) has been associated with hematologic malignancies such as Hodgkin lymphoma, non-Hodgkin lymphoma, and other leukemias. Of all the lymphoid malignancies, MCD is classically associated with Hodgkin lymphoma, occurring in about 1% of Hodgkin's patients. In one case series, the diagnosis of MCD preceded the diagnosis of lymphoma by several months; 71% of patients with Hodgkin lymphoma and MCD had systemic symptoms (i.e. fever, weight loss, and night sweats), and 90% had positive laboratory parameters suggesting an inflammatory syndrome (as assessed by C-reactive protein level, sedimentation rate, and fibrinogen level) [50]. MCD-associated nephrotic syndrome usually relapses simultaneously with the hematologic malignancy and remains highly responsive to specific treatment for the malignancy. MCD can occur at the time of relapse even if it was initially absent, emphasizing the need to evaluate proteinuria during the follow-up of patients with Hodgkin lymphoma.

There is also an association of increased cancer risk in patients with glomerulonephritis (GN). In a recent Danish study in 5594 patients with glomerulonephritis, 911 cancers were diagnosed [51]. Of these, 35% were prevalent at the time of kidney biopsy. Increased cancer rates were seen for: minimal change, focal segmental glomerulosclerosis, mesangioproliferative, membranous, membranoproliferative, ANCA-associated vasculitis, and lupus nephritis. Increased cancer rates were seen for lung, prostate, renal, non-Hodgkin lymphoma, myeloma, leukemia, and skin. The increased incidence was mainly limited to −1 to 1 year after biopsy, but skin cancer showed an increased risk over time. The diagnosis with the highest risk for cancer was membranoproliferative GN.

33.3.3 CKD Associated with Hematopoietic Stem Cell Transplantation (HSCT)

CKD is now an increasingly important complication following HSCT. Hingorani et al. found that CKD was identified in 23% of recipients surviving at least 3 months after HSCT [52]. Acute kidney injury and graft versus host disease (GVHD) were noted as risk factors for the development of CKD. Another study found that the average fall in GFR in patients that develop CKD is 24.5 ml/min/1.73 m^2 over 24 months [53]. Approximately 16.6% patients who underwent HSCT developed CKD (454). Most of these patients were treated with non-myeloablative protocols. The growth in non-myeloablative protocols may actually increase the risk of CKD as older patients with more comorbidities become candidates for this procedure. Calcineurin inhibitors (CNIs), which are used for prophylaxis and treatment of graft versus host disease (GVHD), have been associated with the development of nephrotoxicity and may contribute to the development of CKD. Hypertension (HTN) and TMA are two comorbidities linked to the development of CKD [54–56].

Myeloablative allogeneic HSCT protocols can lead to low grade TMA that over time leads to CKD. This has also been termed bone marrow transplant nephropathy or radiation nephropathy and resembles thrombotic microangiopathies [54]. Clinically, non-nephrotic proteinuria, worsening hypertension, and renal dysfunction are adequate to diagnose TMA in most of these patients. Hypertension is usually the first sign of beginnings of renal limited TMA in many of these cases.

Glomerular disease can be a cause of CKD following HSCT. In HSCT patients with nephrotic-range proteinuria, the renal biopsy findings may include MN, MCD, and FSGS [57]. However, MN accounts for a majority of the cases of HSCT associated glomerular diseases,

while MCD accounts for most of the remaining cases [57]. The etiology and pathogenesis of nephrotic syndrome after allogeneic HSCT were elucidated by Luo et al. [58]. They compared 257 patients with nephrotic syndrome after allogeneic HSCT with non-nephrotic syndrome patients. They concluded that there was association of occurrence of chronic GVHD in patients with nephrotic syndrome after allogeneic HSCT.

33.3.4 CKD Associated with Renal Cell Carcinoma

In the USA, it is estimated that there will be over 64,000 incident cases and 13,700 cancer-related deaths from renal cell carcinoma (RCC) per year [59]. Given the age and comorbid conditions in this patient population, it is not surprising that 25% of patients with RCC have CKD [60]. In fact, approximately 10% of tumor nephrectomy specimens demonstrate features of diabetic nephropathy, 2–9% may have focal segmental glomerulosclerosis, and another 20% show hypertensive nephrosclerosis [61]. In the past, radical nephrectomy was considered the treatment of choice for isolated RCC or solitary renal masses (SRM). However, there is increasing awareness that radical nephrectomy is associated with a higher risk of CKD. Therefore, there has been a shift to partial nephrectomy as the treatment of choice for RCC [62–64]. Huang et al. reported the probability of being free from a GFR less than 60 ml/min/1.73 m^2 5 years after the procedure was 67% and 23% for partial and complete nephrectomy, respectively, with no difference in oncologic outcome [65]. Furthermore, the lower risk of CKD following partial nephrectomy has translated to improved overall survival for patients with localized RCC [65–67]. In a pooled analysis of 41,010 patients, partial nephrectomy was associated with a 61% risk reduction in developing CKD, and 19% risk reduction for all-cause mortality [68]. The American Urological Association released a position statement in 2009 that partial nephrectomy (nephron-sparing surgery) is preferred for T1 tumors (less than 7 cm in size) as the oncologic outcomes are equivalent to radical nephrectomy and the preservation of kidney function is beneficial for long-term outcomes [69]. Most recently, the American Society of Clinical Oncology (ASCO) published guidelines on the management of small renal masses (incidentally image-detected, contrast-enhancing renal tumors ≤4 cm in diameter) that further highlights the recommendation for "nephron-sparing surgeries" such as partial nephrectomy over radical surgical approaches [70]. This guideline recommends that radical nephrectomy should only be considered for patients with anatomically complex small renal masses for whom partial nephrectomy might result in unacceptable morbidity.

A recent study also highlights that "surgically induced CKD" such as that occurring after nephrectomy is more stable than CKD due to medical causes such as diabetes [71]. This is especially true if the postoperative GFR is >45 ml/min/m^2. However, all patients undergoing either partial or radical nephrectomy should have close nephrology follow-up with close attention to treatment of risk factors for CKD progression.

33.3.5 CKD Associated with Paraproteins and Plasma Cell Disorders

Plasma cell disorders encompass a spectrum of diseases that include multiple myeloma, immunoglobulin (Ig)-mediated amyloidosis, plasmacytomas, and the premalignant condition of monoclonal gammopathy of undetermined significance (MGUS). Kidney involvement in these disorders is common and abnormal GFR is seen in up to half of myeloma patients at the time of presentation [72, 73]. Abnormal kidney function in patients with multiple myeloma significantly contributes to excessive mortality and can limit clinical outcomes associated with both systemic therapies and stem cell transplantation (SCT) [73]. Three distinct syndromes account for the vast majority of Ig-mediated kidney disease: (1) cast nephropathy, in which proteinaceous deposits consisting of filtered monoclonal Igs in combination with other urinary proteins (such as

Tamm-Horsfall protein) obstruct the renal tubules as well as elicit an accompanying tubulointerstitial nephritis that typically results in AKI; (2) monoclonal Ig deposition disease (MIDD), characterized by the deposition of monoclonal proteins in the glomerulus and tubular basement membranes leading to local tissue injury; and (3) AL amyloidosis, where monoclonal light chains with specific physiochemical properties form β-pleated sheet structures that deposit in the glomeruli and lead to local tissue injury.

Given the wide spectrum of kidney disease associated with plasma cell disorders, kidney biopsy is recommended when any of these etiologies is suspected. Suspicion should be based upon clinical findings such as fatigue, weight loss, bone pain, and orthostatic hypotension or the presence of autonomic neuropathy coupled with laboratory abnormalities such as anemia, hypercalcemia, proteinuria, Fanconi Syndrome, and a low anion gap (due to the presence of an excess of cationic light chain proteins). Urine dipstick analyses typically do not detect light chains, but tests of total urine protein are abnormal. Thus, a negative urine dipstick test for albumin and the simultaneous detection of significant urine total protein is highly suggestive of light chain proteinuria and requires further testing. Of note, both MIDD and AL amyloidosis typically present with nephrotic-range proteinuria and albuminuria indicative of global glomerular damage.

33.4 Consequences of CKD in Cancer Patients

In the IRMA-2 study, the potential impact of CKD on survival of cancer patients has been assessed on a 2-year follow-up of the patients. The results showed that patients with a GFR lower than 60 mL/min/1.73 m^2 at time of inclusion in the study had a lower survival rate as compared to patients with a GFR greater than or equal to 60 mL/min/1.73 m^2 [74]. In fact, multivariate analysis showed that patients with a GFR lower than 60 mL/min/1.73 m^2 had a mean survival of 16.4 months as compared to 25.0 months for patients with a GFR greater than or equal to 60 mL/min/1.73 m^2 among the whole cohort of patients, whatever the type of tumor and the stage of the cancer disease ($N = 4267$). Considering the 2382 patients who had a nonmetastatic disease, the impact of CKD on survival was still significant with survivals of 21.0 vs. 25.0 months for patients with a GFR lower than or greater than or equal to 60 mL/min/1.73 m^2, respectively. Hazard ratios [95% confidence interval] were 1.27 [1.12–1.44].

In Japan [75] and Korea [76], there also was a significantly reduced survival rate in patients with CKD. In the Korean study, the authors demonstrated that CKD was an independent predictor of cancer-specific mortality, with hazard ratios for death of 1.12 ($p = 0.04$) and 1.75 ($p < 0.001$) for patients with a GFR within 30 and 60 mL/min/1.73 m^2 and below 30 mL/min/1.73 m^2, respectively.

The reasons for the reduced survival of cancer patients with CKD are not fully understood but likely include several factors: (1) comorbid conditions such as diabetes, hypertension, and cardiovascular disease that are independently associated with higher mortality, (2) restricted access to clinical trials due to arbitrary exclusion criteria focus on low GFR, (3) errors in dosing of chemotherapeutic medications (either over- or under-dosing) due to lack of dosing guidelines in CKD patients, and (4) interruptions in therapy due to changes in GFR that may require cessation of medications cleared by the kidney. Clearly, more research is needed to understand this mortality link.

33.5 Risk of Cancer in CKD Patients

Just as cancer and its related therapies may lead to CKD, there is an increased risk of cancer in patients with CKD. There are a number of putative factors which may account for the increased cancer risk in CKD patients, such as defects in immunological functions secondary to uremic state, carcinogenic uremic toxins (nitrosodimethylamine), impaired antioxidant defenses, vitamin

D deficiency, use of erythropoiesis-stimulating agents, cumulative immunosuppression, and risk of acquired cystic kidney disease [77, 78]. More research is needed to clearly understand the links. Wong et al. [79] demonstrated that, over a cohort of 3654 participants, men, but not women, with at least stage 3 CKD had a significantly increased risk for cancer (test of interaction for gender $p = 0.004$). The increased risk of cancer began at a GFR of 55 mL/min/1.73 m^2, and the risk of cancer (mostly lung and urinary tract) was increased by 29% for each 10-ml decline in eGFR (MDRD formula). A Danish registry study conducted over 16 years (1993–2008) reported on the incidence and prevalence of cancer in 823 patients with autosomal dominant polycystic kidney disease (ADPKD) and end-stage kidney disease (ESKD). The authors analyze the data over two 8-year periods of time: 1993–2000 and 2001–2008. The incidence of cancer per year of risk did not change significantly: 3.1% (95% CI 1.8–5.4) in 1993–2000 vs. 2.6% (95% CI 2.1–3.3) in 2001–2008 ($p = 0.4$). However, the average percentage in cancer prevalence gradually increased, from 10.4% (95% CI 8.1–13.3) in 1993–2000 to 14.0% (95% CI 12.8–15.4) in 2001–2008, resulting in a rise of 35% ($p = 0.0002$). Considering yearly prevalences, it almost doubled, from around 8.5 in 1993 to 15 in 2008 [16]. The primary causes of death among the 431 patients who died over the whole period changed when ranked according to the death rates/1000 years on renal replacement therapy. Death rates for cancer and infections did not significantly change between the two periods, while deaths from cardiovascular and cerebrovascular diseases significantly decreased, by 1.5 and 3.6, respectively. This made cancer the third cause of death during the second period (2001–2008). The most frequent cancers in this population were basal cell carcinoma, squamous cell carcinoma of the skin, breast cancer, cancer of cervix uteri, melanoma, and cancers of the colon, respiratory tract, bladder, prostate, and kidney, by descending order of frequency.

The interpretation of usual tumor markers screening tests in ESKD patients is complex due to a high incidence of false-positive results. This highlights the need for clinicians to rely on standard cancer screening recommendations for the population with CKD along with clinical judgment regarding the benefit of screening in a population with a potentially limited longevity [80]. For instance, tumor markers such as cancer antigen 125 (CA 125), carcinoembryonic antigen (CEA), squamous cell carcinoma antigen (SCC), or neuron-specific enolase (NSE) are glycoproteins with a relatively moderate-to-high molecular weight. They are not effectively removed by renal replacement therapies such as hemodialysis or peritoneal dialysis, and they thus may accumulate and be falsely elevated [80]. Stool occult blood testing is also altered by the high incidence of mucosal bleeding and gastric and colonic angiodysplasia in patients on dialysis, and the rate of false-positive is also high.

33.6 Dosing of Chemotherapeutic Medications in CKD

In patients with reduced GFR, the pharmacokinetics of drugs is often modified. Not only the urinary route of elimination is impaired but also the other phases of the pharmacokinetics may be altered by the presence of CKD and uremic retention solutes. These modifications may require dosage adjustments of anticancer medications in patients with CKD and cancer. Most often, these consist of a reduction of the administered dose in order to reduce accumulation, overdosage, and dose-dependent side effects. However, the dose must be at a certain threshold to maintain efficacy. Most often in patients whose GFR is greater than 60 mL/min, there is no need for dose adjustment and the usual dosage can be and should be used. Reducing the dose in these patients will lead to a loss in efficacy. In patients whose GFR is lower than 60, approximately 50% of anticancer drugs require dosage reductions and clinicians should work closely with experienced oncology-trained pharmacists to determine the correct dose.

33.7 Conclusion

In cancer patients, estimating renal function with an appropriate and validated method is mandatory in order to diagnose kidney disease and ensure proper dosage of medications. Understanding the various etiologies of CKD unique to the patient with cancer is also critical to ensure proper diagnosis and therapy. Prevention of a fall in GFR should be a clear goal for all cancer patients since progressive CKD resulting either from the cancer or its treatment leads to a shortened lifespan and negates some of the amazing gains seen with modern advances in cancer treatment.

Before You Finish: Practice Pearls for the Clinician

- A GFR estimate must be calculated in all cancer patients to screen for kidney disease.
- Throughout the course of a patient's cancer treatment, GFR should be periodically assessed and a nephrologist should be involved in the care of patients with eGFR <60 ml/min.
- CKD patients are at a higher risk for a number of cancers. Usual screening protocols may need to be modified in CKD patients since there is a higher frequency of false-positive for several tumor markers.
- A GFR estimate lower than 60.
  - Is an independent risk factor for reduced survival.
  - requires drug dose adjustments for many agents to limit the risk of overdose and toxicity.
- Even drugs with a major non-urinary elimination route may require dose reductions in case of reduced GFR.

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