Chapter 13: CKD as a Complication of Cancer

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CKD AND CANCER: A "CIRCULAR" RELATIONSHIP

CKD is recognized as a disease that may complicate cancer and its therapy. This is in part related to the fact that preexisting CKD is highly prevalent in oncologic patients. Indeed, as observed in the Renal Insufficiency and Anticancer Medications (IRMA)-1 and -2 studies (1,2), more than half of patients with an active malignancy present with an eGFR of <90 mL/min per 1.73 m^2. Furthermore, the prevalence of more severe CKD (*i.e.*, stages 3–5), not requiring dialysis, was 12.0% and 11.8%, respectively (1,2). Similar results have been reported in other series from different countries, thereby confirming that CKD is a relatively common occurrence in cancer patients, irrespective of the type of malignancy. As a whole, causes potentially able to have a negative impact on kidney function are summarized in Table 1.

Interestingly, the relationship between the kidney and cancer appears to be bidirectional (3). For example, preexisting CKD may impact the bioavailability and/or safety profile of an anticancer drug, potentially leading to different and sometimes suboptimal treatment choices. On the other hand, it is also possible that the renal effects of a novel anticancer drug may lead to progressive kidney injury or to worsening of preexisting CKD (3). In addition to the observed increase in CKD prevalence in cancer patients, both CKD and ESRD are risk factors for a number of malignancies (4). However, not all solid tumors appear to be equally represented in this population.

A retrospective cohort study of 1,190,538 adults assessed the association between eGFR level and the risk of incident cancer (5). During 6,000,420 person-years of follow-up, 76,809 incident cancers were identified in 72,875 subjects. After adjustment for time-updated confounders, lower eGFR was associated with an increased risk of renal cancer, with an adjusted hazard ratio (HR) of 2.28 (95% CI, 1.78–2.92) for an eGFR <30 mL/min per 1.73 m^2 (5). The authors also observed an increased risk of urothelial cancer at an eGFR <30 mL/min per 1.73 m^2 but no significant associations between eGFR and other cancers. Finally, CKD conferred an increased cancer-specific mortality in patients with kidney and urinary tract cancer (6). In ESRD patients on dialysis, the observed increased risk for renal parenchymal cancer is related to the development of acquired renal cystic disease, which increases with time on dialysis (7).

CKD and antineoplastic drugs

Acute and chronic kidney injury associated with antineoplastic drug exposure is well described for the classic cytotoxic agents that are used. In addition, there is a large body of literature that describes dosing of these drugs in patients with underlying renal dysfunction and those on dialysis; however, little is known about the appropriate use of the new targeted agents in this population. This creates a complicated issue for oncologists and nephrologists who care for these patients and must provide both safe and effective anticancer therapy. After decades of use of common cytotoxic drugs, clinicians versed in cancer care and its complications are well aware of the main toxicities of these agents. The new, molecularly targeted, anticancer drugs that are entering clinical practice have a wide array of previously unrecognized and ill-defined adverse effects (8). Ultimately, these toxicities must be readily recognized and managed by those providing care for patients exposed to these drugs. This

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Table 1. Causes of kidney disease in cancer patients

Cause	Mechanism(s)
Antineoplastic drugs	
Traditional chemotherapeutic agents	• Direct nephrotoxicity (*e.g.*, cisplatin)
Novel targeted therapies	• Hypertension and/or proteinuria (*e.g.*, VEGF[Rs]-targeted agents) • TMA (*e.g.*, VEGF-targeted agents) • Interstitial nephritis and other glomerulonephritis • Autoimmune nephropathies (*e.g.*, anti-CTLA4 and anti-PD1/PDL1 antibodies) • Indirect toxicities (*e.g.*, nausea/vomiting, diarrhea, dysgeusia) leading to dehydration/volume depletion
Other drugs used in cancer patients	• Direct nephrotoxicity (*e.g.*, NSAIDs, bisphosphonates)
Anti-pain drugs	
Bisphosphonates	
Radiation therapy	• Still ill defined
Contrast medium	• Direct nephrotoxicity
Paraneoplastic renal syndromes	• Autoimmune mechanism?
Nephrectomy	• Loss of nephrons
For cancer	• AKI
For other causes	
Obstruction/compression	• Mechanical injury
Tumor Infiltration	• Kidney infiltration
Comorbid risk factors	• Hypertension • Preexisting CKD • Diabetes mellitus • AKI • Previous use of nephrotoxic cancer therapies

VEGF(Rs), vascular endothelial growth factor (receptors); TMA, thrombotic microangiopathies; CTLA4, cytotoxic T-lymphocyte antigen 4; PD1, programmed cell death 1; PDL1, programmed cell death ligand 1; NSAIDs, nonsteroidal anti-inflammatory drugs.

includes understanding risk factors for targeted drug-induced kidney injury, appropriate drug dosing (if known) for the patient with AKI, CKD, and those on dialysis, the clinical manifestations of drug nephrotoxicity, and the optimal management of nephrotoxic complications (8).

Frequently, oncologists ask their nephrology colleagues to assess the degree of kidney function impairment to provide insight into dosage adjustment of anticancer therapy. To accomplish this, a thorough knowledge of the specific metabolism of anticancer agents and of their pharmacokinetic and pharmacodynamic properties is mandatory. The thought process includes deciding "if" the drug should be administered, "when" it is appropriate to dose the drugs, and to "what extent" dosage adjustment should be used in the setting of underlying kidney disease (3). This approach must be carefully done, as unnecessary treatment interruptions and drug dose reductions may be associated with suboptimal cancer therapy and hamper the clinical benefits of cancer therapy.

Optimal management of underlying CKD and its complications, which may be significantly ameliorated in many cases, as well as prevention of further kidney damage from other exogenous nephrotoxins (*e.g.*, contrast medium, nonsteroidal anti-inflammatory drugs, bisphosphonates) in cancer patients with preexisting CKD, is also key to minimizing drug-related complications. Unfortunately, patients with CDK and those on dialysis are often undertreated for their neoplastic disease due to the fear of drug-induced adverse effects.

Although the relationship between kidney function and cytotoxic agents will be covered in other chapters of the curriculum, the pharmacokinetic properties and specific renal toxicities of novel anticancer agents are summarized in Table 2. The pharmacokinetics of these drugs are similar as most are 90%–98% bound to plasma proteins, and their excretion occurs predominantly via the feces (or the reticulo-endothelial system), whereas urinary excretion is quite variable from one drug to the other (8).

As stated in the drugs' Summary of Product Characteristics (SmPC), the pharmacokinetic properties of the majority of these drugs are not influenced by kidney function (3). A population pharmacokinetic model, which includes data from subjects with baseline creatinine clearance ranging from 30 to 150 mL/min, indicated that it is unlikely that renal insufficiency has a clinically relevant effect on the pharmacokinetics of targeted therapies (9). Thus, no dosage adjustment is recommended in patients with a creatinine clearance >30 mL/min. To date, only patients with adequate kidney function (serum creatinine ≤ 1.5 times the upper limit of normal) have been included in registrative randomized controlled trials. In patients with a creatinine clearance <30 mL/min, a patient population that is poorly studied, caution is recommended (10). Interestingly, this conservative recommendation is not based on data, as drug exposure in patients with severe renal impairment was similar to that observed in patients with normal kidney function (10).

Table 2. Renal toxicities of anticancer targeted agents (modified from reference 3)

Drug	Patients with renal function impairment included in pivotal trial	Renal excretion	Most-frequent renal AEs	Dose reduction required?		
				Patients with mild to moderate CKD	Patients with severe CKD	Patients receiving dialysis
VEGF/VEGFR-tageting agents						
Bevacizumab	No	No	Hypertension, proteinuria	No	No (no data)	No
Aflibercept	No	No	Hypertension, proteinuria	No	No (no data)	No
Sunitinib	No	16%	Hypertension, proteinuria	No	No (no data)	No
Pazopanib	No	<4%	Hypertension, proteinuria	No	No (no data)	No
Axitinib	No	23%	Hypertension, (proteinuria)	No	No (no data)	No
Other multikinase inhibitors						
Sorafenib	No	19%	Hypertension, proteinuria, hypophosphatemia	No	No (no data)	No
Regorafenib	No	19%	Hypertension, proteinuria, electrolyte disorders	No	No (no data)	No data
Vandetanib	No	25%	Hypertension, proteinuria, AKI	No	Yes (few data)	No
Imatinib	No	13%	More renoprotective effects	No	No (no data)	No
mTOR inhibitors						
Everolimus	No	2%	Proteinuria, AKI, electrolyte disorders	No	No (no data); suspend if AKI	No
Temsirolimus	No	4.6%	As for everolimus, but less frequent	No	No (no data); suspend if AKI	No
EGFR inhibitors						
Gefitinib	No	<4%	Electrolyte disorders	No	No (no data)	No
Erlotinib	No	<9%	Electrolyte disorders	No	No (no data)	No
Afatinib	No	<5%	Electrolyte disorders	No	No (no data)	No (no data)
Cetuximab	No	No	Hypomagnesemia, other electrolyte disorders	No	No (no data)	No
Panitumumab	No	No	Hypomagnesemia, other electrolyte disorders	No	No (no data)	No (no data)
B-Raf inhibitors and MEK inhibitors						
Vemurafenib	No	1%	AKI (tubular necrosis?)	No	No (no data)	Possible (risk of arrhythmia)
Dabrafenib	No	23%	Hypophosphatemia, (granulomatous nephritis?)	No	No (no data)	No (no data)
Trametinib	No	<20%	Hypertension, hyponatremia (with dabrafenib)	No	No (no data)	No (no data)
ERBB2-targeting agents						
Trastuzumab	No	No	Hypertension, AKI (with cisplatin)	No	No (no data)	No
Pertuzumab	No	No	No issues	No	No (no data)	No (no data)
Lapatinib	No	2	No issues	No	No (no data)	No
Trastuzumab emtansine	No	<5%	Hypokalemia	No	No (no data)	No (no data)
Antibodies against CTLA4						
Ipilimumab	No	No	Autoimmune nephritis, (drug reaction with eosinophilia and systemic symptom syndrome?)	No	No (no data)	No (no data)
Other agents						
Crizotinib	No	No	Reduction of eGFR (tubular necrosis?), renal cysts	Possible, with caution	Possible, with caution (no data)	No (no data)
Catumaxomab	No	No	No issues	No	No (no data)	No (no data)

AE, adverse event.

CKD postnephrectomy for kidney cancer

Surgical resection remains the gold standard treatment for localized renal cell carcinoma (RCC) and is also commonly performed for synchronous metastatic disease. The type of surgical resection utilized to treat RCC for the last several decades has been radical nephrectomy, although, more recently, increasing emphasis has been placed on the concept of nephron-sparing procedures (11).

Although radical nephrectomy and nephron-sparing surgery do not appear to differ in terms of oncologic outcome, the two different strategies differ in terms of incidence of postoperative CKD and of cardiovascular complications (12). Less invasive surgical procedures for RCC are associated with improved outcomes with less postoperative AKI and CKD and less cardiovascular complications (12). This is not trivial considering that 22% of patients with renal tumors had a pre-nephrectomy stage 3 or greater CKD (eGFR $<$ 60 mL/min per 1.73 m^2) (13). In patients 70 years of age and older, the percentage approaches 40% (13). Overall, among 662 patients scheduled for partial or radical nephrectomy, the prevalence of stage 3 or greater CKD was 26% (14). Furthermore, patients that had postoperative AKI following radical nephrectomy had a 4.24-fold higher risk of developing new-onset CKD (15). Progression of underlying CKD was also noted in patients undergoing a radical nephrectomy procedure for an RCC (15).

Accordingly, both the American Urological Association (16) and the European Association of Urology (17) endorsed partial nephrectomy as the novel standard of care for organ-confined tumors $\leq$4 cm (T1a) and suggested that it be considered as a viable option for patients with tumors $>$4 but $\leq$7 cm (T1b).

Evidence for a relationship between the extent of kidney tissue removal and the risk of CKD comes from single-center retrospective studies, population-based studies, and a single randomized, controlled, phase 3 study (12). Among the population-based studies available between 1990 and 2011, a meta-analysis of 36 studies, of which only one was prospective, examined 31,729 patients treated with radical nephrectomy and 9,281 patients managed conservatively (18). The results demonstrated that partial nephrectomy was associated with a 19% reduction in the risk of all-cause mortality (HR, 0.81; $P<0.0001$), a 29% reduction in cancer-specific mortality (HR, 0.71; $P<0.001$), and a 61% reduction in the risk of severe CKD (HR, 0.39; $P<0.0001$), supporting the findings observed in a number of smaller studies (12).

In contrast to these findings, however, the results of a highly controversial randomized controlled trial, conducted by the European Organization for the Research and Treatment of Cancer (EORTC) (19), complicate the surgical approach to renal cell cancer. In this trial, a more favorable outcome was observed in patients treated with radical nephrectomy compared with those treated conservatively. During a median follow-up of $>$9 years, death occurred in 25% of patients treated by partial nephrectomy and in 18.3% of those undergoing radical nephrectomy. Cardiovascular diseases were noted to be the most common cause of death. The intention-to-treat analysis showed a 10-year overall survival rate of 81.1% in the radical nephrectomy group compared with 75.5% in the partial nephrectomy group (HR, 1.5; 95% CI, 1.03–2.16). Interestingly, partial nephrectomy was associated with a 21% reduction in the absolute risk of developing moderate CKD (eGFR $<$ 60 mL/min per 1.73 m^2) over a median follow-up of 6.7 years, whereas the difference in the incidence of severe CKD (eGFR $<$30 mL/min per 1.73 m^2) between the two groups was 3.7% (19).

These results have generated various hypotheses about the effect of medical- versus surgical-associated CKD on patient survival. It is speculated that medical disease–related CKD has worse outcomes than CKD due to surgery (nephron loss), likely related to other comorbidities and the primary renal disease (*i.e.*, diabetes mellitus). Indeed, a recent report suggested that patients with medical risk factors for CKD are at increased risk of progressive renal impairment, irrespective of the use of partial nephrectomy (20).

The duration of renal ischemia during partial nephrectomy may also play a key role in the development of postoperative CKD. In a recent collaborative review (21), a strong association was noted between the quality and quantity of renal tissue that is preserved after surgery and long-term kidney function, and also the duration of ischemia proved to be an important modifiable predictor of postoperative kidney function. Prolonged warm ischemia time (WIT) proved to be significantly associated with adverse postoperative kidney function (21). Available data suggest a renal benefit of keeping WIT $<$25 minutes (21). Conversely, cold ischemia appears to safely allow longer durations of ischemia (21).

Finally, patients with CKD (irrespective of its cause) within the setting of a metastatic cancer usually tolerate cancer-targeted agents poorly, experiencing higher-grade adverse events compared with patients with normal kidney function (3).

Tumor-induced CKD

End-stage cancer is often associated with malignant ureteral obstruction (MUO), leading to obstructive nephropathy and CKD. Direct ureteral infiltration by tumor or extrinsic ureter compression by bulky tumor masses frequently cause these sequelae (22). In general, cervical, bladder, and prostate cancers are the most common culprits (22). However, urinary obstruction can also occur from retroperitoneal fibrosis due to surgery, chemotherapy, and/or radiotherapy.

In the setting of malignant obstruction, percutaneous nephrostomy tube placement or retrograde ureteral double-J stent placement should be urgently performed, recognizing the associated procedural complications (22). Recently, a prognostic model for survival after palliative urinary diversion for malignant urinary obstruction has been developed (23). Two risk factors (at least four events related to malignancy and an Eastern Cooperative Oncology Group [ECOG] index $\geq$2) were used to stratify patients into three groups by survival type: favorable (no factors), intermediate (one factor), and unfavorable (two factors). The median survival at 1, 6, and 12 months was 94.4%, 57.3%, and 44.9% in the favorable group, 78.0%, 36.3%, and 15.5% in the intermediate group, and 46.4%, 14.3%, and 7.1% in the unfavorable group, respectively (23). This simple model could help to guide clinical decisions when choosing which patients are reasonable candidates for urinary diversion in a palliative setting.

CONCLUSION

CKD is highly prevalent in oncologic patients and appears to be a risk factor for the development of cancer. Furthermore, the use of antineoplastic drugs in patients with underlying CKD raises several specific issues: 1) the direct nephrotoxicity of several anticancer agents (especially novel molecularly targeted agents); 2) the need to adjust antineoplastic doses due to concomitant CKD; 3) the lack of prospective drug dosing data in patients with advanced CKD or those on dialysis; and 4) the nihilistic approach to the treatment of this population of patients with CKD, leading to the frequent undertreatment (or even absence of treatment) of these patients, ultimately denying them potentially life-prolonging options (3). Indeed, in our opinion, CKD should not be regarded, in and of itself, as a reason to reduce or hold targeted therapies in the absence of other comorbidities or medical indications (3).

TAKE HOME POINTS

- The relationship between CKD and cancer should be regarded as bidirectional.
- The use of targeted agents in cancer patients with CKD is ill defined.
- CKD and ESRD requiring dialysis, *per se*, should not be regarded as reasons not to administer anticancer treatments.
- Nephrectomy for kidney cancer is another common cause of CKD, but the use of nephron-sparing surgical techniques have been developed to limit this issue.
- Medical disease–related CKD has worse outcomes than CKD due to surgery.
- The tumor may cause CKD by causing urinary obstruction with obstructive nephropathy.

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REVIEW QUESTIONS

1. Which types of cancer are more commonly observed in CKD patients?

   a. Gastrointestinal cancers
   b. Lung cancers
   c. Breast cancers
   d. Renal and urothelial cancers

Answer: d is correct. A large retrospective cohort study assessed the association between eGFR level and the risk of incident cancer. Lower eGFR was associated with an increased risk of renal cancer with an adjusted HR of 2.28 (95% CI, 1.78–2.92) for an eGFR $<$30 mL/min per 1.73 m^2. An increased risk of urothelial cancer at an eGFR $<$30 mL/min per 1.73 m^2 was also evidenced. Finally, CKD conferred an increased cancer-specific mortality in patients with kidney and urinary tract cancer.

2. Should the dose of a targeted anticancer agent be reduced in a patient with mild to moderate CKD?

   a. Yes, almost always
   b. No, almost never
   c. Yes, depending on the drug's pharmacokinetic properties
   d. The targeted anticancer agent should not be used in this setting

Answer: b is correct. The pharmacokinetics of all targeted anticancer agents are similar. Most are 90%–98% bound to plasma proteins, and their excretion occurs predominantly via the feces (or the reticulo-endothelial system), whereas urinary excretion is quite variable among the drugs. A population pharmacokinetic model indicated that it is unlikely that renal insufficiency has a clinically relevant effect on the pharmacokinetics of targeted therapies. Thus, no dosage adjustment is recommended in patients with a creatinine clearance $>$30 mL/min.

3. Which of the following contributes to the development of CKD in nephrectomized patients?

   a. Nephrectomy itself (loss of nephrons)
   b. Concomitant comorbidities
   c. Ischemia time
   d. All the above

Answer: d is correct. Radical nephrectomy and nephron-sparing surgery greatly differ in terms of incidence of postoperative CKD, due to the different amount of nephron loss. Less invasive surgical procedures for renal cell carcinoma are associated with less postoperative AKI and CKD. Despite this, a recent report suggested that patients with medical risk factors for CKD are at increased risk of progressive renal impairment, irrespective of the use of partial nephrectomy, thus highlighting the key role played by comorbidities in the development of post-nephrectomy CKD. The duration of ischemia is another important predictor of postoperative kidney function. Prolonged warm ischemia time is significantly associated with adverse postoperative kidney function.