Chronic Kidney Disease and Cancer

31

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Before You Start: Facts You Need to Know

- Chronic kidney disease (CKD) is highly prevalent in the general population and also in cancer patients.
- Cancer prevalence is higher in the CKD population, for a number of tumors. 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.
- There are specific rules and processes to manage drugs, and especially anticancer drugs, in patients with CKD.
- Nephrotoxic drugs should be avoided, whenever possible, in patients presenting with preexisting renal impairment. In some cases, for a similar expected efficacy, several drugs may be used, among which the less nephrotoxic should be chosen. This applies, for instance and in some circumstances, to platinum salts (cisplatin being more nephrotoxic than carboplatin which is more nephrotoxic than oxalipatin) and intravenous bisphosphonates (zoledronate being more nephrotoxic than pamidronate which is more nephrotoxic than ibandronate).

31.1 Introduction

Screening for chronic kidney disease (CKD) in cancer patients is an emerging question, and this is crucial for several reasons. The first reason is the direct consequence of the better oncological care delivered to those patients which has now made cancer a chronic disease, at least for some solid tumors for which the increasing efficacy of treatments and the increasing number of treatments available, and thus the multiplication of treatment lines, allow significant survival rates for patients. In those patients, early diagnosis of CKD is a priority so that they can benefit from the advances in nephrology care. Such advances can slow the progression in the reduction of kidney function, i.e., the glomerular filtration rate (GFR), thus sparing the need for dialysis in a number of patients who will not reach the terminal stage of CKD. Furthermore, it has been clearly demonstrated that CKD is an independent risk factor for cardiovascular disease and

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cardiovascular mortality. With the increasing survival of cancer patients, the prevention of cardiovascular morbidity and mortality has become an issue, and this requires early diagnosis of CKD. In addition, some anticancer treatments, such as anthracyclines, may also exhibit a cardiac toxicity, which may be more preoccupating in patients already at risk for cardiovascular events. The second reason is pharmacological. In patients with reduced GFR, the pharmacokinetics of drugs are modified. Adjusting drug doses to renal function is mandatory to avoid overdose and overdose-induced side effects. The pharmacokinetics and tolerance profiles for anticancer drugs are often modified in patients with CKD. In those cases, screening for abnormal GFR and adjusting anticancer drug doses allow better tolerance with maintained efficacy (see Chap. 27).

31.2 Screening for CKD in Cancer Patients

31.2.1 Evaluation of Kidney Function in Cancer Patients

Routinely measuring the actual GFR with a gold standard method such as ^{51}Cr-EDTA in all cancer patients is unrealistic. As a result, such as in the general population, it is recommended to calculate GFR from serum creatinine (SCr), with recommended formulae (see Chap. 2). In this purpose, only considering the raw value of SCr is misleading. In fact, the same SCr value may reflect totally different GFR depending on the production rate of creatinine in a particular patient, essentially from muscle catabolism. Calculating GFR (or creatinine clearance (CrCl) which is assumed to be an acceptable estimate of the GFR) with the two formulae recommended allows an appropriate evaluation of kidney function. The Cockcroft-Gault formula [1] still is the most used formula to calculate CrCl. A more recently released formula is the Modification of Diet in Renal Disease (MDRD) study formula [2].

Both formulae do not present with the same performance in terms of precision in estimating the GFR, as compared to a measured GFR, with a gold standard method. In particular, there are some special populations of patients in whom the Cockcroft-Gault formula may result in false estimates and should not be used. Those populations include patients older than 65 and patients with a body mass index greater than 30, i.e., the obese. Contrarily, the MDRD formula allows a precise estimation of the kidney function of the patient. Furthermore, in some recent studies specifically conducted in patients with cancer, the MDRD formula confirmed its better precision as compared to Cockcroft-Gault in those patients [3, 4], and it has been recommended to estimate cancer patients' kidney function with this formula, even in elderly cancer patients [5].

Once the estimation of kidney function has been performed, CKD should be defined by its stage (1–5) even in cancer patients rather than with the "ancient" terminology using terms such as "moderate" or "severe."

Particular attention should be paid to the units of the results in GFR estimates, especially when attempting to compare the performances of different formulae. On one hand, the MDRD formula gives an estimate of the GFR in mL/min/1.73 m^2. On the other hand, Cockcroft-Gault and other formulae give results in mL/min. As a result, any comparison between formulae requires prior conversion of the raw results of calculations into the same units. There are, unfortunately, a number of published studies in which such conversions were not made. Their results and conclusions can thus not be considered.

In clinical practice, estimates in both units are needed for a particular patient. The estimate in mL/min/1.73 m^2 is mandatory to diagnose CKD and stratify its stage since the international definition is based on GFR estimates expressed in this unit. The estimate expressed in mL/min is also needed to determine the precise level of kidney function (i.e., value of the GFR) to determine the adjusted dose of medications the patient will be administered. This is of a particular importance for anticancer drug management, which requires a precise dose: neither too high nor too low.

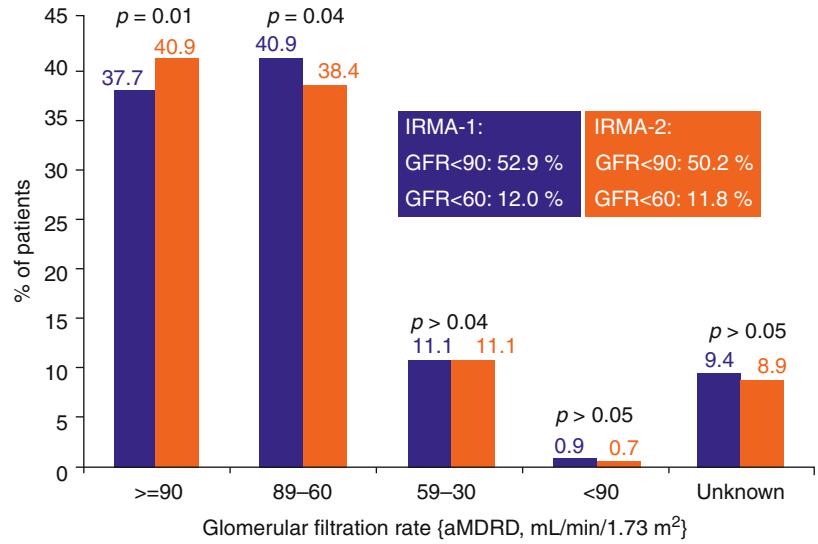

Fig. 31.1 Prevalence of kidney disease in cancer patients: IRMA-1 and IRMA-2 results

31.2.2 Prevalence of Kidney Disease in Cancer Patients

In France, two studies have recently been conducted in order to evaluate the prevalence of CKD in cancer patients, only with solid tumors, excluding patients on dialysis. Those studies called "IRMA" (Insuffisance Rénale et Médicaments Anticancéreux – Renal Insufficiency and Anticancer Medications) both demonstrated the high prevalence of CKD in those two cohorts of about 5,000 patients each [6, 7] (Fig. 31.1).

Adult patients, not on dialysis, and with a diagnosis of cancer were included in the studies. Demographical, biological, clinical, and pharmacological data were collected. Patients' kidney function was estimated with the MDRD formula. The average age of the patients was 58.1 and 59.4 years, respectively, in IRMA-1 and IRMA-2. Patients presented with different types of tumors, mainly breast, colorectal, and lung, and approximately half of them were nonmetastatic at the time of inclusion.

The prevalence of an elevated serum creatinine (SCr) value was low, and strictly the same in both studies: 7.2 % of the patients had a SCr greater than or equal to 110 µmol/L (around 1.25 md/dL). However, when the kidney function of those patients was estimated with the MDRD formula, 52.9 and 50.2 % of the patients in IRMA-1 and IRMA-2 respectively, had in fact a reduced GFR (lower than 90 mL/min/1.73 m^2) and 12.0 and 11.8 % had stage 3 or more CKD (lower than 60 mL/min/1.73 m^2) (Fig. 31.2).

In patients with kidney cancer, the study of Huang et al. is particularly interesting. The authors reported a prevalence of abnormal kidney function (lower than 90 mL/min/1.73 m^2) of 87 % in a cohort of 662 patients with a renal cortical tumor (<4 cm) and awaiting partial or radical nephrectomy. The prevalence of a GFR lower than 60 mL/min/1.73 m^2 was also high, higher than the one we reported in the IRMA studies, with 26 % of the patients with a stage 3–4 kidney disease [8]. The authors then further demonstrated that, in addition to this high prevalence of abnormal renal dysfunction prior nephrectomy, the GFR at baseline was highly predictive of developing CKD after the nephrectomy had been performed. For these reasons, evaluating kidney function with the MDRD formula is mandatory in every cancer patient, and also in kidney cancer patients.

Other studies also retrieved high prevalences of CKD in cancer patients, in Belgium [9], the United States [10], and Japan [11]. In these studies, the prevalence of a GFR lower than 60 mL/min/1.73 m^2 ranged from 16.1 to 25.0 % of patients presenting with a variety of solid tumors.

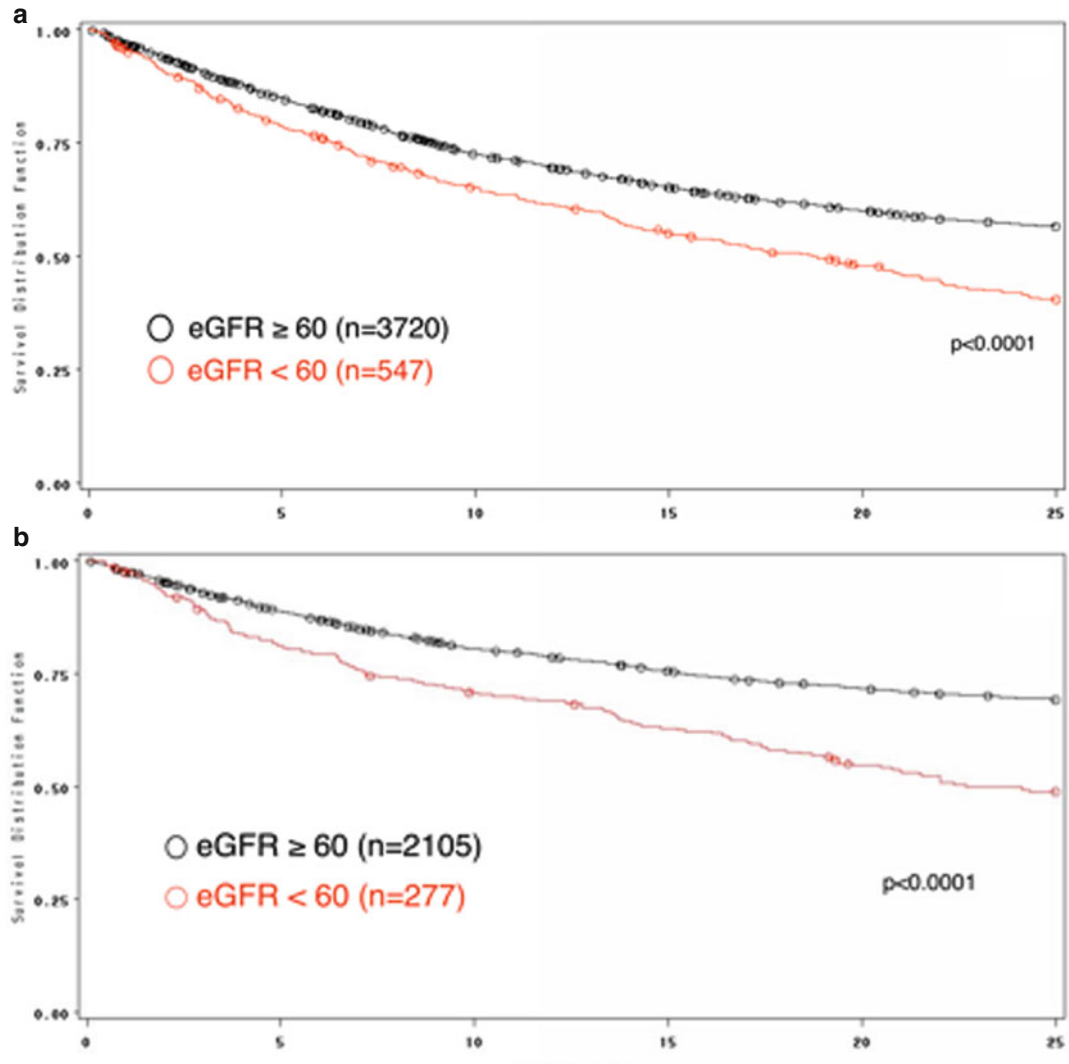

Fig. 31.2 Survival rate in IRMA-2 patients with cancer according to baseline GFR at inclusion. (**a**) All patients ($n=4267$) and (**b**) nonmetastatic patients ($n=2382$)

31.3 Consequences of Kidney Disease in Cancer Patients

31.3.1 Impact on Patient Survival

In the IRMA-2 study, the potential impact of CKD on patient survival 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 [12] (Fig. 31.3). In fact, multivariate analysis adjusted for several factors, including the age, 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 ($N=4,267$). Considering the 2,382 patients who had a non-metastatic 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,

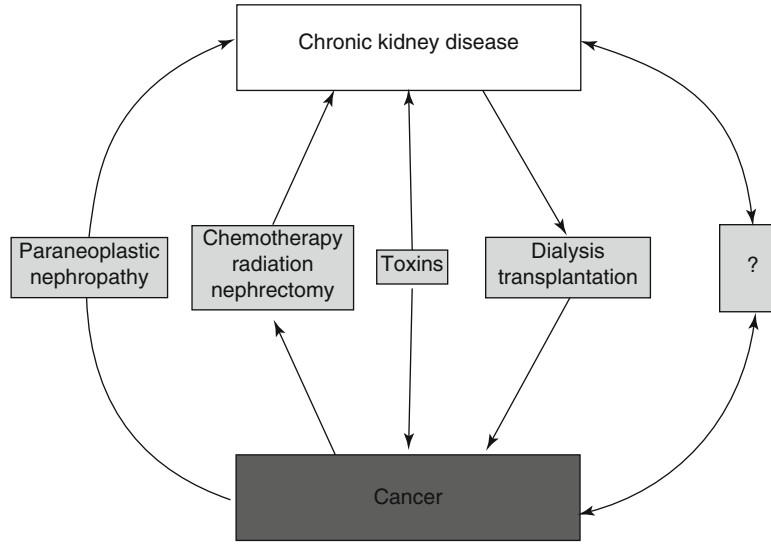

Fig. 31.3 Various pathways linking chronic kidney disease and cancer

Table 31.1 Multivariate analysis on the risk of death according to the level of renal function at inclusion in the IRMA-2 study

Population	Median survival (months)		Hazard ratio [CI 95 %] (Cox model)
	GFR ≥ 60	GFR < 60	
All patients (n = 4,267)	25.0*	16.4*	1.27** [1.12–1.44]
Nonmetastatic patients (n = 2,382)	25.0*	21.0*	1.42*** [1.17–1.72]

IRMA Insuffisance Rénale et Médicaments Anticancéreux *(Renal Insufficiency and Anticancer Medications)*, *GFR* glomerular filtration rate, *CI* confidence interval
*p < 0.0001; **p < 0.0002; ***p < 0.0003

respectively. Hazard ratios [95 % confidence interval] were 1.27 [1.12–1.44] (p = 0.0002) and 1.43 [1.17–1.72] (p = 0.0003) for the whole population and the nonmetastatic population only, respectively (Table 31.1).

In Japan [11] and Korea [13], other authors reported 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.

31.4 Incidence of Cancer in Kidney Disease Patients

There are multiple pathways which may link cancer and CKD [14], and the other side of the coin is the potentially higher incidence of cancers in patients with kidney disease. Wong et al. [15] demonstrated that, over a cohort of 3,654 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 higher risk began at 55 mL/min/1.73 m^2, and the risk of cancer (mostly lung and urinary tract, not prostate) 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 (APKD) and end-stage renal disease (ESRD). 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

Table 31.2 Unadjusted death rates from the primary causes of death in Danish patients with ADPKD and ESRD

	Time periods		
	1993–2000	2001–2008	*P*
Cardiovascular disease	40.3	26.4	<0.01
Cerebrovascular disease	17.1	4.8	<0.001
Infections	12.1	16.8	NS
Cancer	8.1	12.3	NS

Source: Reprinted from Orskov et al. [16] by permission of Oxford University Press
APKD autosomal dominant polycystic kidney disease, *ESRD* end-stage renal disease, *NS* not significant

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/1,000 years on renal replacement therapy (Table 31.2). 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.

Other sources suggest a number of factors which may account for 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 [17]. The interpretation of usual tumor markers screening tests in ESRD patients appears to be tricky due to a high incidence of false-positive results. 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. On the opposite, alpha-fetoprotein, beta-human chorionic gonadotropin (HCG), and prostate-specific antigen (PSA) seem to be reliable. Stool occult blood testing is also altered by the high incidence of mucosal bleed and gastric and colonic angiodysplasia in patients on dialysis, and the rate of false-positive is also high. In practice, cancer screening protocols need to be modified/adjusted for ESRD patients since they may not be useful as such in these patients.

Finally, in polypathological patients, there is evidence that patients may be at increased risk for cancer, due to sequential and parallel mechanisms, e.g., diabetes. Diabetic patients are known to be at risk for developing CKD. As a result, the prevalence and the incidence of CKD in these patients are higher than in nondiabetic. Other evidence showed that these patients also present with a higher risk for cancer, especially for liver, pancreas, and endometrial cancers but also for breast, colon, kidney, and bladder cancers, of which incidences may be increased by 20–50 % as compared to nondiabetics [18].

This also emphasizes why evaluating and monitoring kidney function is also important to identify potential at-risk patients for cancer.

31.4.1 Practical Consequences on Anticancer Drugs' Handling

In patients with reduced GFR, the pharmacokinetics of drugs is most often modified. Not only the urinary route of elimination is impaired but also the other phases of the pharmacokinetics. 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

saccumulation, overdosage, and dose-dependent side effects. However, the dose must not be too much reduced 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 must 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. Taxanes and anthracyclines usually do not require any dose modification in CKD. In contrast, platinum salts cisplatin and carboplatin require dosage adjustment, while it is not the case for oxaliplatin. Cyclophosphamide and ifosfamide may require dose reductions, but only in patients with a GFR lower than 15 mL/min. Capecitabine will require a reduction in the dose as early as the GFR is lower than 60 mL/min.

31.5 Handling of Targeted Therapies in Patients with CKD

In a recent study on the pharmacokinetics of sunitinib in patients with renal insufficiency, the authors observed a lower exposure to sunitinib in CKD patients as compared to patients with normal kidney function, suggesting a lower absorption of sunitinib from the gastrointestinal tract in patients with CKD, and thus a risk for lower exposure and lower efficacy [19].

Vandetanib is a recently approved tyrosine kinase inhibitor indicated in the treatment of aggressive and symptomatic medullary thyroid cancer. It acts on the vascular endothelial growth factor receptor 2 (VEGFR-2), the epidermal growth factor receptor (EGFR), and the RET tyrosine kinase. The drug has been shown to be eliminated via hepatic metabolism and biliary excretion as its major route of elimination, with minor urinary excretion, accounting for less than 25 % of the total elimination of the drug. However, the pharmacokinetics of vandetanib was not altered in patients with moderate-to-severe hepatic impairment, whereas significant modifications were reported in patients with renal impairment [20]. These modifications resulted in a nearly doubled exposure to vandetanib in patients with severe renal impairment as compared to patients with normal kidney function. As mentioned in the summary of product characteristics (SmPC) of the drug, total body clearance may be reduced by 30 % and area under the concentration-time curve (AUC) may be increased by 1.5–2-fold in case of renal impairment, thus requiring dose adjustment in patients with a GFR within 30–60 mL/min, to avoid overdose and toxicity. So far, no recommendation has been made for patients with a lower GFR.

Furthermore, for drugs that are almost completely degraded by the liver, the potential activity and toxicity of the metabolites have to be considered, those latter often being secondarily excreted in the urine. This is the case for the majority of tyrosine kinase inhibitors, for instance, sunitinib, sorafenib, erlotinib, and lapatinib. However, data are lacking on their pharmacokinetics, parent drug and metabolites, in patients with CKD. It is important to note that, according to available data, the pharmacokinetics of therapeutic monoclonal antibodies (rituximab, bevacizumab, trastuzumab, denosumab, cetuximab, panitumumab, etc.) are not significantly modified in patients with CKD. They thus can be used at their usual dose, whatever the level of the GFR.

This is a crucial issue in oncology. The IRMA studies demonstrated the high prevalence of CKD in patients with cancer. They further demonstrated that, in "real life," most patients received anticancer drugs that necessitated dose adjustment in case of CKD. Indeed, in the IRMA-1 study, patients were treated with a total number of 7,181 prescriptions of 75 different anticancer agents. 79.9 % of the patients received at least one drug which dose must be adjusted in case of CKD, and 80.1 % of the patients received at least one anticancer drug which may be toxic to the kidneys, which are highly vulnerable in case of preexisting CKD.

Conclusion

In cancer patients, estimating renal function with an appropriate and validated method (like MDRD) is mandatory in order to diagnose kidney disease. In patients with a reduced

GFR, specific attention should be paid to the cardiovascular system, with baseline and periodic evaluations, especially in case of anticancer treatments with potential cardiac toxicities, such as anthracyclines. Anticancer drugs' handling in those patients also requires specific evaluation. In all patients with a GFR lower than 60 mL/min, dose adjustment must be considered. Reliable and updated sources of information should be used. These latter should be evidence-based since official informations provided in drugs' SmPCs often lack precision and clarity regarding this specific topic (Box 31.1).

Box 31.1. Drug Dose Adjustment in CKD Patients: A Practical Approach

Service ICAR (Information Conseil Adaptation Rénale) is a medical advisory service offered to French nephrologists, hematologists, and oncologists, among other specialties, developed in France in 1999 as part of the Department of Nephrology of Pitié-Salpêtrière University Hospital in Paris. Physicians and clinical pharmacists of Service ICAR are available on call to help retrieve information on drug dose adjustment in patients with CKD and determine the appropriate dose of a drug, for a particular patient, based on an exhaustive literature analysis. A website has been developed in 2010 (SiteGPR® – ww.sitegpr.com) which provides healthcare professionals with evidence-based recommendations on drug dose adjustment. Recommendations are available in French and English languages.

Before You Finish: Practice Pearls for the Clinician

- A GFR estimate must be calculated with the MDRD equation in all cancer patients to screen for kidney disease.
- 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 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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