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Renal insufficiency and cancer treatments

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ABSTRACT

Renal insufficiency has been shown to be highly prevalent in patients with cancer. This renal insufficiency has been reported to be associated with reduced overall survival and increased cancer-related mortality. Therefore, it is important to screen patients with cancer for renal insufficiency, using an adequate and reliable method of estimation of the renal function. Renal insufficiency may influence 1 or several of the 4 pharmacokinetic phases (absorption, distribution, metabolism, elimination/excretion), potentially resulting in marked modifications of the pharmacokinetic profile of a drug in patients with renal insufficiency. Consequently, it is potentially necessary to adjust the dosage of anticancer drugs in case of renal insufficiency in order to avoid drug accumulation and in order to reduce overdosage-related side effects. This dosage adjustment of anticancer drugs should be performed according to the level of renal function and with an appropriate and validated method. It is not always easy to find clear information on anticancer drug handling in these patients. However, several guidelines, publications and handbooks are available on how to adjust anticancer drug dosages in patients with renal insufficiency and will help practitioners to manage anticancer drugs in such patients.

INTRODUCTION

For the past 10 years, increasing evidence showed that renal insufficiency (RI) was highly frequent in patients with cancer, especially in patients presenting with solid tumours. Recent data revealed the link between RI and reduced overall survival, while other studies showed an association between RI and increased cancer-related mortality. Anticancer drug handling in these patients with a reduced glomerular filtration rate (GFR) also is an issue, raising the question of drug dosage adjustment. As a result, the clinical care of patients with cancer and RI requires specific attitudes and competencies to provide optimal therapeutic and clinical care. This review will detail the recent data on survival of patients with RI and cancer with emphasis on the most useful advices and tips for clinical practice.

RI IN PATIENTS WITH CANCER: PREVALENCE AND IMPACT ON SURVIVAL

The first studies which reported on the prevalence of RI in patients with cancer were the ‘IRMA studies’ (*Insuffisance Rénale et Médicaments Anticancéreux*—Renal Insufficiency and Anticancer Medications). These two cohorts included about 5000 adult patients each, only patients with solid tumours (mainly breast, colorectal and lung, and approximately half of them were non-metastatic at the time of inclusion), not on dialysis.^{1 2} In these cohorts, 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 m²), and 12.0% and 11.8% had stage 3 or 4 RI (lower than 60 mL/min/1.73 m²). Interestingly, patients with cancer rarely present with a normal GFR, with only 38.6% of patients with breast cancer,³ 38.9% of patients with lung cancer,⁴ 38.3% of patients with prostate cancer,⁵ 27.5% of patients with gynaecological cancer (personal data from the IRMA-1 study) and 27.2% of patients with colorectal cancer (personal data from the IRMA-1 study) having a GFR \geq 90 mL/min/1.73 m² (figure 1). Several other studies reported on the prevalence of RI in patients with cancer. For instance, in patients with kidney cancer, Huang and colleagues reported a prevalence of abnormal renal function (lower than 90 mL/min/1.73 m²) of 87% in a cohort of 662 patients with a renal cortical tumour (<4 cm) and awaiting partial or radical nephrectomy. The prevalence of a GFR lower than 60 mL/min/1.73 m² was also higher than the one reported in the IRMA studies, with 26% of the patients with stage 3–4 RI.⁶ Other studies in Belgium,⁷ the USA,⁸ Japan⁹ and Austria¹⁰ reported prevalences of a GFR<60 of 16.1%, 22.0%, 25.0% and 14.7–16.1%, respectively.

In the IRMA-2 study, the potential impact of RI on patient survival has been assessed through a 2-year follow-up of the patients. The results showed that patients with a GFR lower than 60 mL/min/1.73 m² at the time of inclusion in the study had a lower survival

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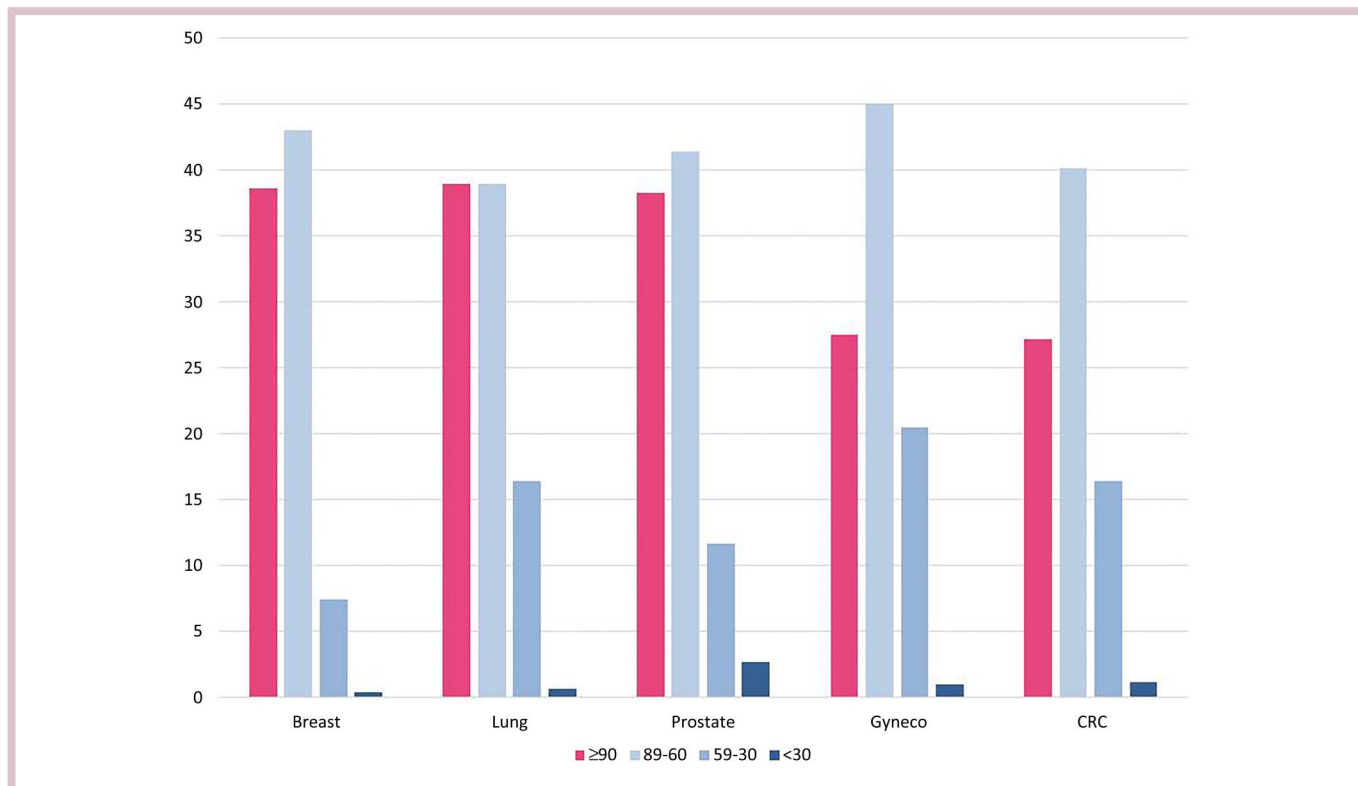


Figure 1 Levels of renal function in patients with cancer. CRC, colorectal cancer.

rate as compared with patients with a $\text{GFR} \geq 60 \text{ mL/min/1.73 m}^2$.¹¹ In fact, multivariate analysis adjusted for several factors, including age, showed that patients with a GFR lower than $60 \text{ mL/min/1.73 m}^2$ had a mean survival of 16.4 months as compared with 25.0 months for patients with a $\text{GFR} \geq 60 \text{ mL/min/1.73 m}^2$ among the whole cohort of patients, whatever the type of tumour or the stage of the cancer disease ($N=4267$). Considering the 2382 patients who had a non-metastatic disease, the impact of RI on survival was still significant with survivals of 21.0 vs 25.0 months for patients with a GFR lower than or $\geq 60 \text{ mL/min/1.73 m}^2$, respectively. HRs (95% CI) were 1.27 (1.12 to 1.44) and 1.43 (1.17 to 1.72) for the whole population and the non-metastatic population only, respectively (table 2). In Korea¹² and Australia,¹³ a link between RI and an increased cancer-related mortality has been found, with HRs of 1.12 (for a GFR between 30 and 60) and 1.75 (for a $\text{GFR} < 30$) in Korea, and 1.27 ($\text{GFR} < 60$) in Australia. In the latter study, each decrease of $10 \text{ mL/min/1.73 m}^2$ was significantly associated with an 18% increase in cancer-related mortality.

Recently, two studies showed the importance of anticancer drug dosage adjustments in those patients with a GFR lower than 60. In the first study, Chen *et al*¹⁴ included 143 patients with metastatic colorectal cancer. All patients had normal serum creatinine (Scr) at inclusion and were all treated the same, at the usual dosage of chemotherapy. After treatment, the renal function was estimated; patients were grouped depending on

whether they had at inclusion a renal function lower or >60 , and safety and survival (time to progression) were compared between groups. Of note, 35% of the patients in this study had a renal function below 60 in spite of a normal Scr. Patients with RI experienced statistically significantly higher rates of dose-related adverse events, which lead to significantly rates of treatment discontinuation or interruption, and significantly reduced time to progression. In another study in elderly patients with early breast cancer, Lichtman *et al*¹⁵ screened for RI in 619 patients who were then treated at dosages adjusted to their level of renal function, when dose reduction was required. When comparing the group of patients with a GFR lower than 60 (treated at adjusted doses) and the group of patients with a $\text{GFR} > 60$ (treated at usual doses), there was no significant effect on RI on relapse-free survival or overall survival. These two studies emphasised the importance of adjusting anticancer drug dosages to renal function when patients have RI.

SCREENING FOR RI IN PATIENTS WITH CANCER

Measuring the actual GFR with a gold standard isotopic method such as $^{51}\text{Cr-EDTA}$ in all patients with cancer is unrealistic. As a result, in the general population, it is recommended to estimate the GFR from Scr with validated formulae. The Cockcroft-Gault formula (CG)¹⁶ has been the most used formula for decades. One major drawback is that CG estimates the creatinine clearance (CrCl) and not the GFR . Furthermore, in the elderly, in

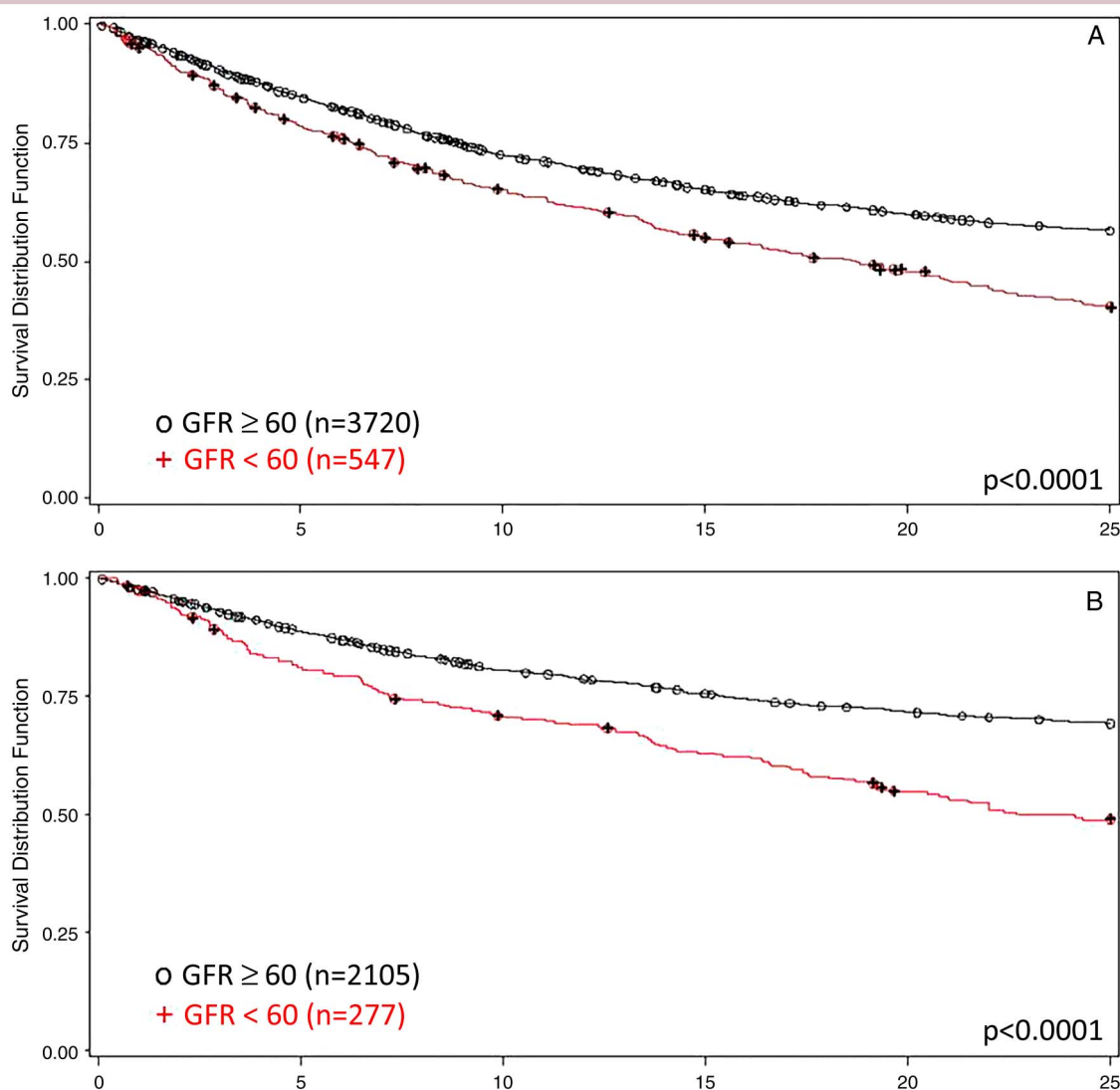


Figure 2 Survival rate in IRMA-2 patients with cancer according to baseline GFR at inclusion: all patients ($n=4267$; A), and non-metastatic patients ($n=2382$; B). GFR, glomerular filtration rate ($\text{mL}/\text{min}/1.73 \text{ m}^2$); IRMA, *Insuffisance Rénale et Médicaments Anticancéreux*—Renal Insufficiency and Anticancer Medications.

the obese and especially in patients with RI, CrCl differs from GFR due to several factors such as the production rate of creatinine or the tubular secretion of creatinine. CG is no longer recommended, and should not be used anymore. Two recent equations have been released. The first one, the Modification of the Diet in Renal Disease equation, under its abbreviated formulation with four variables (MDRD), is still recommended for GFR estimation.¹⁷ The recent Chronic Kidney Disease—Epidemiology collaboration equation (CKD-EPI) currently is the method of choice for GFR estimation, screening and diagnosis of RI.¹⁸ Furthermore, in some recent studies specifically conducted in patients with cancer, the MDRD equation confirmed its better precision as compared with CG in those patients,¹⁹ and it has been recommended to estimate the renal function of patients with cancer with this formula, even in elderly patients with cancer.^{20–21} However, data are still lacking

on the performance of CKD-EPI, especially in patients with cancer; it probably can be used safely since it previously demonstrated its better precision as compared with MDRD in patients without cancer.

Once the estimation of renal function has been performed, the US National Kidney Foundation (KDOQI—Kidney Disease Outcomes Quality Initiative)²² and the international working group KDIGO (Kidney Disease: Improving Global Outcomes)²³ have defined and stratified the severity of chronic RI or kidney disease (KD). This international definition should also be used in patients with cancer (table 1).

PRACTICAL CONSEQUENCES ON ANTICANCER DRUG HANDLING

In patients with reduced GFR, the pharmacokinetics of drugs are most often modified. The urinary route of

Table 1 International definition and stratification of kidney disease by the KDOQI and the KDIGO

Stage	Description	GFR
Patients at increased risk	Risk factors for kidney disease (eg, diabetes, high blood pressure, family history, older age...)	More than 90
1	Kidney damage and normal GFR	More than 90
2	Kidney damage and mild decrease in GFR	60–89
3	Moderate decrease in GFR	30–59
4	Severe decrease in GFR	15–29
5	Kidney failure (dialysis or kidney transplant needed)	<15

Signs of kidney damage may include proteinuria, haematuria, etc. GFR, glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; KDOQI, Kidney Disease Outcomes Quality Initiative.

elimination is impaired, as well as the other phases of the pharmacokinetics.

Drugs pharmacokinetics in patients with KD

The pharmacological effect of a drug depends on its concentration at its site of action, generally a tissue receptor. The pharmacokinetic profile of a drug is based on the evolution of its plasma or total blood concentration along with time after administration, whatever the route of administration. Indeed, plasma and blood are easy-accessible compartments since samples are simply withdrawn by venous puncture. Four pharmacokinetic phases are defined through which a drug may go when administered to a participant. First is absorption, where a drug passes from its site of administration into the central compartment: the serum. The second phase is called distribution during which the drug diffuses in peripheral tissues called compartments, such as the bone and fat tissues, of the central nervous system, for instance. The third phase is metabolism that happens to be hepatic, renal, spontaneous in blood, intracellular and enzymatic or not. The fourth phase is elimination from the body in the urine, bile or faeces. Those four phases are usually called ADME pharmacokinetic phases. It is obvious that those phases are not strictly successive but interdependent. When a drug is

Table 2 Multivariate analysis on the risk of death according to the level of renal function at inclusion

Population	Median survival (months)		HR (95% CI) (Cox model)
	GFR \geq 60	GFR<60	
All patients (n=4267)	25.0*	16.4*	1.27 (1.12 to 1.44)**
Non-metastatic patients (n=2382)	25.0*	21.0*	1.42 (1.17 to 1.72)***

*p<0.0001; **p<0.0002; ***p<0.0003. GFR, glomerular filtration rate (mL/min/1.73 m²).

administered intravenously, there is no absorption phase because it is directly injected into the central compartment. However, when administration is performed with an intravenous infusion, a predistribution phase appears and is no longer called the 'absorption phase' but the 'entry phase'. Renal impairment may influence one or several of these phases, potentially resulting in marked modifications of the pharmacokinetic profile of a drug in patients with RI.^{24 25}

Absorption

Absorption of drugs depends on many factors such as the type of membranes to pass through between the site of administration and blood, the local blood flow rate, the surface of the absorption window and the time during which a drug is in contact with the absorption zone/window. In patients with RI, many variations of these parameters may happen and influence the absorption phase of a drug.²⁶ Intestinal metabolism may also be impaired. Indeed, downregulation of intestinal cytochrome P450 has been reported in rats with chronic renal failure.²⁷ Thus, the quantity of a drug that attains systemic circulation can be significantly impaired in patients with RI. In a recent study on the pharmacokinetics of sunitinib in patients with RI, the authors observed a lower exposure to sunitinib in patients with KD as compared with patients with normal renal function, suggesting a lower absorption of sunitinib from the gastrointestinal tract in patients with KD, and thus a risk for lower exposure and lower efficacy.²⁸

Distribution

A pharmacokinetic parameter that describes a drug's distribution is volume of distribution (Vd). Vd is a mathematical image that reflects the virtual volume in which a drug is able to diffuse when administered. This property gives it the possibility to be very important, larger than total body fluids in some cases, for example, when a drug penetrates into deep compartments such as the skeleton or adipose tissues. A drug's volume of distribution may be affected by variation of protein binding: when the latter decreases, more free drug is available to diffuse in deeper compartments and, as a result, Vd increases. Indeed, protein binding of drugs may be affected in patients with RI, as a consequence of hypoalbuminaemia and higher α 1-glycoprotein serum levels, which are frequent in those patients, and that respectively increases the free fraction of acid drugs and decreases the free fraction of basic drugs. Several studies identified some specific compounds that accumulate in patients with KD and are called 'uraemic toxins', which are suspected to interfere with drugs binding to plasma proteins.^{29–31}

Metabolism

Drugs which are mainly or totally eliminated through hepatic metabolism may also have their pharmacokinetics modified in patients with KD. In fact, a number of hepatic reactions involved in drugs'

biotransformations are affected in KD. Though it has been considered until recently that drugs whose elimination did not involve the kidney have their pharmacokinetics unaltered in the presence of RI, it has now been assessed that some biliary-excreted drugs and drugs that are metabolised by P450 cytochrome enzymes may, however, have their elimination altered in those patients.^{32 33} Furthermore, for drugs that are almost completely degraded by the liver, the potential activity and/or toxicity of the metabolites has to be considered, those latter often being secondary eliminated in urine.

Elimination/excretion

Well defining the terms of elimination and excretion is mandatory to understanding how a drug disappears from the organism. Elimination is the irreversible loss of the drug from the site of measurement, for example, central compartment. Elimination occurs by two processes, excretion and metabolism. Excretion is the irreversible loss of a chemically unchanged drug. As a result, a drug may be eliminated by the liver and its metabolites excreted in the urine. Consequently, the kidney plays an important role in the elimination of most drugs because it is involved in the excretion of the unchanged drug and/or its metabolites.

Renal excretion occurs by two main mechanisms: glomerular filtration and tubular secretion. Drugs that are excreted by glomerular filtration will of course have their excretion reduced in KD, due to the reduction in the GFR of those patients. Tubular secretion is an active mechanism that implies different types of transporters depending on the drugs' characteristics. The three major families of transporters are the organic anion transporters, the organic cation transporters and the transporters of uncharged molecules, which show similarities with P glycoproteins. In patients with KD, both excretion mechanisms may be altered.

Drug dosage adjustment in patients with KD

Those modifications of the pharmacokinetics of drugs in patients with KD expose the patients to overdosage when the dosage is not appropriately adjusted to the patient's renal function. In fact, administering a normal dose of a drug to a patient in whom the elimination processes are impaired exposes the patient to a high risk for overdosage-related side effects, which can be severe in some cases, especially with anticancer drugs. Adjusting anticancer drug dosage in patients with KD is thus necessary to avoid overdosage and tolerance issues, which in turn may question the possibility of repeating the course of the chemotherapy, for instance.

This is a crucial issue in oncology. The IRMA studies demonstrated the high prevalence of KD in patients with cancer. They further demonstrated that, in 'real life', most patients received anticancer drugs that necessitated dosage adjustment in case of KD. Indeed, in the IRMA-1 study, patients were treated with a total number of 7181 prescriptions of 75 different anticancer agents.

In total, 79.9% of the patients received at least one drug whose dosage must be adjusted in case of KD, 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 pre-existing KD.

Dosage adjustment of anticancer drugs should then be performed according to the stage of KD diagnosed in a particular patient. Some guidelines are available on how to adjust anticancer drug dosages in patients with KD. Some of them have been published,^{34 35} and prescription handbooks are also available.^{36 37} The study clearly shows the importance of a thorough assessment of renal function in every patient with cancer, and at each course before administering the drugs. GFR should be estimated by using the aMDRD formula, even when SCr appears to be within the normal range.

REGULATIONS AND CLINICAL TRIALS

The European Medicines Agency (EMA) recently issued an updated version of their guidelines to the industry on when and how to conduct specific trials in patients with RI. The full recommendation can be downloaded from the EMA website³⁸ and is officially applicable since 1 July 2016. These guidelines emphasise that such studies should be conducted for drugs whatever their elimination pathway, including drugs which are hepatically metabolised, since (1) RI can also impair liver function in terms of drug metabolism, and (2) hepatic metabolites can be excreted via the renal route, which can be impaired in patients with RI. They also provide practical recommendations, so that studies share a common methodology and can provide the same level of information for clinical use. Owing to the high prevalence of RI reported in patients with cancer, such studies should be conducted in every new drug developed in the field of cancer. This should be considered as mandatory. In addition, new studies are needed for existing drugs, following this newly recommended methodology, in order to know when it is necessary to adjust a drug dosage, and how.

CONCLUSION AND PRACTICAL RECOMMENDATION

- ▶ In patients with cancer, estimating renal function with an appropriate and validated method (aMDRD) is mandatory in order to diagnose KD and improve anticancer drug handling in those patients.
- ▶ When a patient has a $GFR < 60 \text{ mL/min/1.73 m}^2$:
 - Nephrotoxic drugs should be avoided whenever possible. In some cases, for a similar expected efficacy, several drugs may be used, among which the less nephrotoxic ones should be chosen. This applies, for instance in some circumstances, to platinum salts (cisplatin being more nephrotoxic than carboplatin, which is more nephrotoxic than oxaliplatin) and intravenous bisphosphonates (zoledronate being more nephrotoxic than pamidronate, which is more nephrotoxic than ibandronate).

- When a nephrotoxic drug is mandatory, specific methods to prevent renal toxicity must be used, as recommended for cisplatin, for instance.³⁹
- The question of dosage adjustment should be asked for every anticancer drug, whatever the route of elimination, whatever the potential renal toxicity. Dosage adjustment aims at reducing the overdosage-related side effects and not only the renal side effects of drugs.

Competing interests None declared.

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