EXPERT OPINION ON DRUG METABOLISM & TOXICOLOGY, 2017
VOL. 13, NO. 6, 617–623
https://doi.org/10.1080/17425255.2017.1292252

Taylor & Francis
Taylor & Francis Group

REVIEW

Pharmacokinetic/pharmacodynamic considerations for cancer patients undergoing hemodialysis

Nicolas Janus[a,b] and Vincent Launay-Vacher[a,b]

[a]Service ICAR, Pitié-Salpêtrière Hospital, Paris, France; [b]Nephrology Department, Pitié-Salpêtrière Hospital, Paris, France

ABSTRACT

Introduction: The increased incidence of cancer in hemodialysis patients has been discussed since the mid-70s. Today, physicians regularly encounter situations where they must manage the prescription of anticancer drugs in hemodialysis patients.

Areas covered: Hemodialysis patients are at risk of dose-related toxicities due to pharmacokinetic modifications. Hemodialysis patients are at risk of therapeutic drug removal during their hemodialysis session, which may result in a loss of efficacy. In the advent of novel immunotherapies, particularly tumor vaccines, there is an increased theoretical risk of pharmacodynamic modification. Indeed, pharmacodynamic modifications have already been reported for viral vaccines.

Expert opinion: It is important to consider all of the potential pharmacokinetic/pharmacodynamic modifications before prescribing anticancer drugs in hemodialysis patients. However, pharmacokinetic/pharmacodynamic modification should not be considered a contraindication for anticancer drug use in hemodialysis patients, rather, clinicians should be aware of the need individualize treatment according to available recommendations.

ARTICLE HISTORY
Received 22 June 2016
Accepted 3 February 2017

KEYWORDS
Hemodialysis; anticancer drugs; pharmacodynamic; pharmacokinetic

1. Introduction

Although renal transplantation is considered to be the best 'treatment' for hemodialysis (HD) patients, HD is still the commonest 'treatment' for these patients. Over one million people worldwide benefit from long-term dialysis. The number of patients under dialysis increases by at least 5% per year in Western countries due to aging and increasing prevalence of type II diabetes, a condition that is frequently associated with the deterioration of renal function.

Many studies in the past have shown that the risk of cancer development is increased in HD patients when compared with the general population [1–6]. Cancer and chronic kidney disease (CKD) are connected especially in HD patients, and HD may be a risk factor of cancer [7]. In addition, mortality from cancers was reported to be higher in HD patients than in the general population [8,9]. The postulated pathogenic mechanisms for cancer development in HD patients include: altered DNA repair, impaired immune system function, decreased antioxidant defense, chronic infection and inflammation, and accumulation of carcinogenic compounds [9,10]. The result is that more and more physicians are facing the question of anticancer drugs handling in HD patients, because of the potential pharmacokinetic/pharmacodynamic (PK/PD) modifications of these drugs in this population. In fact, it was illustrated by one study. The authors reported that most dialysis patients received anticancer drugs that need dosage adjustment because of pharmacokinetic modifications [11]. The same study also reported that most patients received anticancer drugs that could be removed by HD session, exposing them to an under-dosage.

2. Pharmacokinetic modifications

2.1. Absorption

Anticancer drugs can be administered intravenously (IV) (chemotherapies for example) and also orally (sunitinib, sorafenib, erlotinib, etc.). For anticancer drugs administered IV, there is no intestinal absorption. However, for oral anticancer drugs, pharmacokinetic modifications of the absorption were reported [12].

Many physiological (Figure 1) changes could occur: changes in gastric pH that could affect the absorption of some oral drug by changing their state of ionization. Changes in the integrity of the intestinal wall in HD patients have also been reported with increased gut permeability because of inflammatory conditions [13,14]. Furthermore, a decrease in the activity and expression of intestinal and hepatic enzymes responsible for drug metabolism has been reported in CKD patients, thus inducing a reduction of the effects of hepatic first-pass [15,16].

Consequently, the quantity of a drug that attains systemic circulation can be significantly impaired in HD patients. For example, in a 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

CONTACT Nicolas Janus nicolas.janus@psl.aphp.fr Service ICAR - Department of Nephrology, Groupe Hospitalier Pitié-Salpêtrière, 47-83 Boulevard de l'Hôpital, 75013 Paris

Article highlights

- Cancer and chronic kidney disease are connected and especially in hemodialysis.
- More and more physicians are facing the question of anticancer drugs handling in hemodialysis patients.
- Hemodialysis patients are facing two different problems: (1) a risk of overdose because of the kidney failure and (2) a risk of inefficiency because of the removal of the anticancer drugs by the hemodialysis session.
- Most of anticancer drugs need dosage adjustment in hemodialysis patients because of pharmacokinetic modifications.
- Many anticancer drugs need a specific timing of administration according to the hemodialysis session.

This box summarizes key points contained in the article.

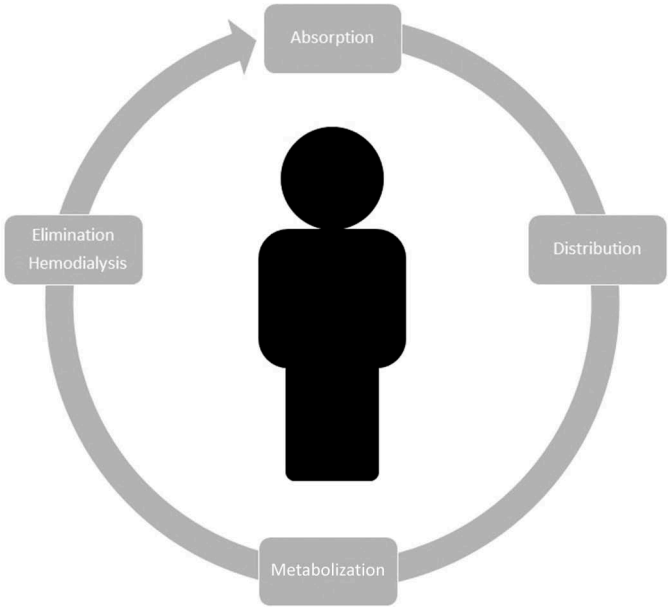

Figure 1. Pharmacokinetic modifications in chronic kidney disease patients.

with normal renal function, suggesting a lower absorption of sunitinib from the gastro-intestinal tract in patients with a kidney disease and thus a risk for lower exposure and lower efficacy [17].

2.2. Distribution

Next is the second phase, called distribution, during which the drug diffuses into peripheral tissues called compartments, such as the bone, fat, and tissues of the central nervous system. During the distribution, many drugs are binding on plasma proteins (albumin, etc.). However, in CKD patients, hypoalbuminemia is frequent. Furthermore, CKD can result in changes in plasma protein binding of drugs, an effect that has particular importance for highly bound drugs [12,18,19]. Consequently, the unbound fraction of the drug is increasing, leading to potential overdosage and dose-related side effects. For example, hypoalbuminemia could lead to potential overdosage of cisplatin and paclitaxel [20]. Indeed, cisplatin is strongly linked to albumin (>90%). In a study in patients with hypoalbuminemia lower than 30 g/L versus healthy patients, the authors reported an increase in toxicities related to treatment with cisplatin and paclitaxel (anemia, fatigue, neuropathy, and loss of appetite) [21]. The binding of paclitaxel to plasma proteins such as albumin is important for achieving its therapeutic target. Albumin binds paclitaxel and transports it in the bloodstream, allowing its gradual liberation, thus decreasing its toxic effects [21].

Another example, the area under the curve of the unbound SN-38 (7-ethyl-10-hydroxycamptothecin) (an active metabolite of irinotecan) in CKD patients was 4.38-fold higher than that in normal kidney patients. The unbound fraction of SN-38 was also 2.6-fold higher in such patients, partly because SN-38 protein binding was displaced by the uremic toxin 3-carboxy-4-methyl-5-propyl-2-furanpropionate. The authors also reported that this result was supported by the correlation of the unbound fraction of SN-38 with the plasma 3-carboxy-4-methyl-5-propyl-2-furanpropionate concentration, which negatively correlated with renal function [22].

Finally, the volume of distribution of drugs is potentially significantly increased in CKD patients [12,23], because of fluid overload.

2.3. Metabolism

Pharmacokinetic studies in HD patients have shown that non-renal clearance is reduced for many drugs [12,19]. For example, vandetanib has a very low hepatic extraction ratio, indicating that intrinsic hepatic clearance and plasma protein binding are the most important determinants of hepatic clearance. However, hepatic dysfunction appeared to have no significant effect on either intrinsic hepatic clearance or plasma protein binding [24,25]. However, CKD was reported to increase the exposure of vandetanib [24,25]. An explanation is that uremic toxins that accumulate in HD patients modify the activities of metabolizing enzymes and also of the hepatocyte transporters [26,27]. However, this effect could lead to different consequences according to the profile of the drug. For example, some drugs used are administered as an inactive form (pro-drugs) and are metabolized by the liver into an active form. In this case, CKD patients' liver will not be able to generate the active compound of the drug. Consequently, the patients will accumulate the inactive compound, and the treatment will not be efficient. For example, fluorouracil (5-FU) is mostly metabolized in the liver and renal excretion accounts for less than 10% [28]. Several observations indicated that 5-FU may be used at its usual dosage in patients with HD [29]. Capecitabine is a non-cytotoxic fluoropyrimidine carbamate, which functions as an orally administered precursor of the cytotoxic moiety fluorouracil. Capecitabine is activated via several enzymatic steps. It is first metabolized by hepatic carboxylesterase to 5′-DFCR (5'-deoxy-5-fluorocytidine), which is then converted into 5′-DFUR (5'-deoxy-5-fluorouridine) by cytidine deaminase, principally located in the liver and tumor tissues. Further catalytic activation of 5′-DFUR then occurs by thymidine phosphorylase. The enzymes involved in the catalytic activation are found in tumor tissues but also in normal tissues, albeit usually at lower levels. The sequential enzymatic biotransformation of capecitabine to fluorouracil leads to

higher concentrations within tumor tissues and consequently to the pharmacological effects. The renal impairment had no effect on the pharmacokinetics of capecitabine but leads to an increase in the systemic exposure to two metabolites, the 5′-DFUR and the alpha-fluoro-beta-alanine [30]. Following the administration of capecitabine, 5′-DFUR is the direct precursor of fluorouracil and alpha-fluoro-beta-alanine is the final metabolite of fluorouracil. Neither metabolite is cytotoxic, but the exposition to 5′-DFUR is correlated to safety. However, no data are available for HD patients.

2.4. Elimination/excretion

It is mandatory to clearly define the terms 'elimination' and 'excretion' to understand how a drug disappears from the organism. Elimination is the irreversible loss of drug from the site of measurement. Elimination occurs by two processes, excretion and metabolism. Excretion is the irreversible loss of 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. It is therefore very important to follow all the compounds of the administered drug.

There are three different mechanisms of renal excretion: glomerular filtration, tubular secretion, and tubular reabsorption. Unbound fraction of drugs and small size drugs are eliminated by the glomerular filtration. Secretion and tubular reabsorption are implicating active transport mechanisms and involve different transporters. In HD patients, these three mechanisms are impacted. In chronic dialysis patients, the renal function is considered to be null and it will not improve. In such cases, the only way is renal transplantation. The consequence is an accumulation of the drug with potential dose-related side effects. For example, cisplatin is mainly eliminated through the kidney (90%) [31].

Nephrotoxicity is no longer a limitation in HD patients, but patients remain exposed to potential dose-related side effects, such as anemia and neuropathy. The dose of cisplatin must, therefore, be reduced in HD patients. In HD patients, cisplatin clearance is similar to that observed in patients with normal renal function after a single administration of 30 mg.

However, a significant fall of the clearance of the free fraction of cisplatin has been reported in one HD patient [32]. Several studies have demonstrated good efficacy and tolerance of cisplatin in HD patients. One HD patient received four cisplatin infusions of 25 mg/m^2 in two courses and underwent HD session before each treatment [33]. In another study, cisplatin was given in HD patients at a dose of 50 mg, four administrations every 15 days, followed by two administrations of 80 mg. The plasma concentration was never >3.16 µg/ml [34]. Five other HD patients received cisplatin at various doses [35]: two patients started cisplatin at the initial dose of 40 mg/m^2 followed by injections of 80 mg/m^2 and three at the dose of 80 mg/m^2 upfront. Tolerance to cisplatin in all these patients was similar to that in patients with normal renal function. Finally, the initial doses of cisplatin in HD patients must be reduced by 50%, at a recommended dose of 25–50 mg/m^2 every 3–6 weeks [12]. Furthermore, cisplatin is highly and irreversibly bound to plasmatic proteins [24]. Free cisplatin is dialyzable and the loss of free cisplatin during HD is not compensated by bound cisplatin. Therefore, cisplatin must be given following HD sessions or on non-dialysis days.

2.5. Drug transporters

Several studies have reported that the activity of uptake and efflux transporters, expressed in the small intestine, the kidney, and the liver, is altered in chronic renal failure [26,27,36,37].

For example, the protein expression of the intestinal efflux transporters P-gp and MRP2 (Multidrug Resistance Protein 2) is decreased in rats with chronic renal failure, whereas the expression of the influx transporters OATP2 and OATP3 is not affected. In the liver, however, protein expression of P-gp and OATP2 is reduced, whereas MRP2 expression is not affected by chronic renal failure. These results indicate that chronic renal failure can affect the expression of drug transporters differently in the liver compared to the intestine [12].

3. Hemodialysis

Most dialysis patients are treated with chronic HD. The aim of the HD session is to replace the renal function by removing toxic wastes. Usually, HD patients performed three sessions, of 4 h each, per week. But it is possible to perform HD session daily. However, HD session can also remove anticancer drugs prematurely and be responsible for a potential under-dosage and therapeutic inefficiency. Therefore, HD patients are facing two different problems: (1) a risk of overdose because of the kidney failure and (2) a risk of inefficiency because of the removal of the anticancer drugs by the HD session. In such patients, the dose and the timing of administration according to the HD session are very important. In fact, the CANDY (CANcer and DialYsis) study reported that 72% of the patients received at least one anticancer drug that required a dosage adjustment or for which there were no data in dialysis patients. Furthermore, 82% had at least one anticancer drug requiring administration after HD sessions [11]. For daily drugs, it is easy to specifically administer before or after the session. However, in case of BID (twice a day) or TID (three times a day) administrations, it is harder to organize the optimal timing of administration according to the HD session.

The timing of administration (before/after HD session) is not the only problem. For example, several chemotherapies are continuously administered (like fluorouracil) for several days. But, in this case, some HD sessions may overlap the fluorouracil administration and, because the fluorouracil is dialyzable [29], could therefore expose the patient to a potential inefficacy. In theory, in such cases, it could be wise to stop the continuous administration of the fluorouracil during the HD session and to resume it after the end of the HD session. However, no published study confirmed this theory.

HD session could also be an opportunity. For example, gemcitabine is rapidly deaminated after administration to an inactive metabolite: 2′,2′-difluorodeoxycytidine (dFdU). The renal elimination of gemcitabine and its metabolites accounts for <10% and

for 90% of the administered dose, respectively [38]. The use of gemcitabine in HD patients has been found to be safe [38,39]. However, a 5- to 10-fold prolongation of its elimination half-life and a higher area under the curve (AUC) of dFdU were measured in HD patients [39] and may induce side effects. While gemcitabine removal by HD has never been studied, it is known that dFdU is removed by HD session. It is therefore recommended to start HD sessions 6–12 h after gemcitabine administration to minimize the potential side effects of dFdU [29,40]. Consequently, it is important to adapt the dosage of drugs in HD patients when necessary (Table 1). Several methods are available: (1) the 'dose method,' which reduces the dosage and maintains the dosing interval; (2) the 'interval method,' which increases the interval between two administrations but with a standard dosage; and (3) the 'mixed method,' which uses both (1) and (2).

4. Pharmacodynamic modifications

Pharmacodynamic modifications in HD patients are not common. The pharmacodynamic properties of chemotherapies and targeted therapies are not impacted by CKD. But it is important to consider potential pharmacodynamic modifications, because it was reported to be impaired for other drugs, like SGLT2 inhibitors and vaccines.

The SGLT2 (sodium-glucose co-transporter 2) transporter, expressed in the proximal renal tubules, is responsible for the majority of the reabsorption of filtered glucose. Diabetic patients have been shown to have elevated renal glucose reabsorption which may contribute to persistent elevated blood glucose concentrations. By inhibiting SGLT2, these drugs reduce reabsorption of filtered glucose and lower the renal threshold for glucose and thereby increase urinary glucose excretion. In CKD patients, the urinary glucose excretion is decreased; therefore, SGLT2 inhibitors will not work [42]. However, no anticancer drugs presented such mechanisms.

HD patients are immunocompromised [43]. This immune dysfunction is the consequence of an impaired cell-mediated and humoral immunity, reducing activities of the immune system cells (B-cell, T-cell, monocytes, macrophages, etc.). Consequently, impaired immune responses to vaccination (hepatitis B virus vaccination, etc.) have been reported since 1992 [44], and it is necessary to potentially modify the dosage of vaccines in HD patients. Therefore, the question of the efficacy of immunotherapy is rising. Recent successes with drugs targeting T-cell inhibitory molecules have led to a significant increase in enthusiasm for immunotherapy [45]. Generally, immunotherapy is a treatment designed to enhance a patient's immune response against their tumors. There are multiple forms of immunotherapy, which include: (1) checkpoint blockade, the class of drugs targeting T-cell inhibitory molecules; (2) adoptive cellular therapy, which involves direct infusion of T cells into patients; and (3) vaccines, which are a form of active immune therapy designed to stimulate the patient's immune system to recognize tumor cells as foreign [45]. These tumor vaccines used various strategies to generate immune responses, commonly targeting specific and purported tumor-associated antigens instead of antigens unique to a patient's tumor. However, in all cases, the tumor vaccines were based on a 'seroconversion' of the patients. Therefore, questions arise: What would happen in immunocompromised HD patients? Would the immune dysfunction of HD patients compromise the mechanisms of these tumor vaccines? Would higher and/or supplemental booster doses be necessary and efficient?

Table 1. Most prescribed cytotoxic drugs in the IRMA (Insuffisance Rénale et Médicaments Anticancéreux) study.

	Need for dosage adjustment in hemodialysis patients according to	
INN	Janus et al. [29]	Lichtman et al. [41]
5-FU	No	No
Capecitabine	No data	No data
Carboplatin	Yes	Yes
Cisplatin	Yes	Yes
Cyclophosphamide	Yes	Not mentioned in the recommendations
Docetaxel	No data	No data
Doxorubicin	No	No data
Epirubicin	No data	No
Etoposide	Yes	Yes
Gemcitabine	No	No data
Irinotecan	No data	No data
Methotrexate	No data	No data
Oxaliplatin	No data	No data
Paclitaxel	No	No
Vinorelbine IV	Yes	No data

INN: international non-proprietary name; 5-FU = 5-fluorouracil.

5. Consequences

Several studies reported the impact of CKD on the mortality in cancer patients. In fact, CKD was reported to be an independent risk factor of a reduced overall survival in cancer patients [46]. Furthermore, two studies also reported that CKD was an independent predictor factor of cancer-specific mortality [47,48]. Finally, every 10 ml/min/1.73 m^2 fall was associated with an 18% increase in cancer-related mortality [48]. This reduced survival has been hypothesized to be related to the cardiovascular complications of CKD or as a consequence of inappropriate drug dosage adjustment [46]. Recently, two studies helped us to check one of these hypotheses. Chen et al. reported higher toxicities and a lower progression-free survival in CKD patients receiving chemotherapies (capecitabine and carboplatin) in metastatic colorectal cancer (mCRC) patients in comparison to patients without CKD [49]. Because CKD patients were not identified, chemotherapy doses were not adjusted to renal function. A second study included patients treated by CMF (cyclophosphamide, methotrexate, fluorouracil, AC (doxorubicine, cyclophosphamide), and capecitabine for breast cancer [50]. CKD patients received specific doses according to their renal function. The authors reported that the overall survival and the relapse-free survival were not statistically different after a follow-up period of 12 years in CKD patients versus non-CKD patients. Of course, these two studies were not comparable (for example, mCRC vs. breast cancer patients) and the treatments were not the same. However, it underlined that not adjusting the doses of anticancer drugs in CKD patients was exposing CKD patients to a higher mortality and that drug dosage adjustment in CKD

cancer patients was found to be effective and comparable to full doses in non-CKD cancer patients. However, there is no such study published for HD patients.

6. Drug–drug interactions

Drug–drug interactions (DDIs) can be classified into two groups: pharmacokinetic and pharmacodynamic. In pharmacokinetic DDIs, the pharmacokinetic properties (absorption, distribution, metabolism, or excretion) of a drug are altered by another drug. A common pharmacokinetic interaction concerns drugs metabolized by the cytochrome P450 (CYP) enzymes. By inhibition or induction of CYP iso-enzymes, blood and tumor concentrations, antitumoral effects, and toxicities of specific anticancer therapies may be altered. Other pharmacokinetic interactions may result from, for example, inhibition of the ABCB1 efflux transporter (or P-glycoprotein); by altering the activity of ABCB1, the bioavailability of anticancer drugs may be influenced [51]. In pharmacodynamic DDIs, an additive, synergistic, or antagonistic effect occurs when two drugs are used concomitantly [52]. For example, pharmacodynamic DDIs can be beneficial (e.g. enhanced pharmacologic effects with fluorouracil and leucovorin), but may also be potentially harmful (e.g. ototoxicity with furosemide and cisplatin) [51]. The number of comorbidities and the number of over the counter drugs used concomitantly with anticancer drugs were identified as potential determinants for performing an intervention [52]. In case of potential DDI, it is important to consider the risks before stopping a treatment and to search for an alternative if necessary and if possible.

7. Food–drug interactions

Food–drug interactions (FDIs) are for oral anticancer drugs. It may increase or decrease the systemic exposure of these drugs. For example, high-fat meals can decrease C_{max} and AUC values of afatinib by 50% and 39%, respectively [53]. On the contrary, high-fat meal increased C_{max} and AUC values of cabozantinib by 41% and 57%, respectively [53]. Furthermore, grapefruit also increases blood levels of drugs by inhibition of the hepatic metabolism, exposing patients to dose-related side effects. Therefore, it is important to give some recommendations and advice to patients taking drugs.

8. Renal transplant patients

Renal transplant is the only 'treatment' for HD patients. However, they are still considered as CKD patients. These patients are exposed to two more problems: (1) DDI with immunosuppressive drugs (cyclosporine and tacrolimus) and (2) renal toxicities of all drugs, including anticancer drugs.

9. Conclusion

Anticancer drugs used in HD patients are a growing concern as these patients are exposed to an increased risk of cancer [7]. However, because of their renal condition, oncologists may be reluctant to treat these patients. It is a fact that most of anticancer drugs need dosage adjustment in HD patients and need a specific timing of administration according to the HD session. But, specific recommendations [29] and tools [54] to treat such patients are available.

Finally, it is also important to consider the potential pharmacodynamic modifications of anticancer drugs, but it seems that it may potentially concern only the future anticancer vaccines.

10. Expert opinion

Most drugs require a specific renal management in HD patients, in terms of drug dosage and time of administration regarding the HD session. Indeed, the clinical risks for the HD cancer patients are: (1) developing extra-renal toxicity because of the increase in drug systemic expositions and (2) having inefficient drug exposure because of early extensive elimination throughout dialysis. In order to prevent these two problems, it is crucial to use the available recommendations and tools to treat such patients adequately. All kinds of drugs are concerns, not just anticancer drugs.

10.1. Key findings

HD cancer patients are first of all cancer patients and these patients deserve to have a treatment. It is important to consider all the potential pharmacokinetic/pharmacodynamic modifications before treating them with anticancer drugs. HD is not an absolute contraindication to anticancer drugs in itself. Despite the fact that each patient and each clinical context is unique, it is essential to propose an adapted anticancer drug strategy (doses, timing, and monitoring) to HD patients (whenever possible) rather than contraindicating it systematically. Unfortunately, the main finding of this work is that PK/PD clinical data are very rare.

10.2. What do we need?

We clearly need adequate and dedicated studies on end-stage-renal disease (ESRD) patients. Because it represented an industrial risk to include such patients, most of the drug industry excluded CKD patients and more specifically ESRD patients. However, because of the increasing incidence of cancer in ESRD patients, physicians are facing the growing matter of the management of anticancer drugs in these patients. We need dedicated studies in ESRD patients with old and new drugs. This includes both pharmacodynamic and pharmacokinetic studies.

10.3. What is going to happen?

In 2015, the European Medicines Agency (EMA) issued an updated version of their guidelines to the industry on when and how to conduct specific trials in CKD patients and is officially applicable since 1 July 2016. These guidelines emphasize that such studies should be conducted for drugs whatever their elimination pathway. They also provide with practical recommendations, so that studies share a common methodology and can provide the same level of information for clinical

use. Due to the high prevalence of CKD reported in cancer patients, such studies should be conducted in every new drug developed in the field of cancer. The EMA specifically stated that: 'For drugs that may need to be administered to ESRD patients undergoing dialysis treatment and where the drug or active metabolites are likely to be extracted during dialysis to such an extent that supplementary dosing after dialysis treatment may be required, pharmacokinetic evaluation of the contribution of dialysis treatment to the elimination of the drug and potentially active metabolites in ESRD patients is recommended.' Furthermore, the EMA stated that 'if a clinically relevant effect on the pharmacokinetics of the drug is observed in haemodialysis patients, pharmacokinetic studies should also be considered in subjects on other dialysis regimens such as ambulatory peritoneal dialysis and continuous renal replacement therapy (CRRT), if the drug is likely to be used in such patients.'

In other words, the EMA recommended performing clinical trial in (potentially) all dialysis patients. Unfortunately, these recommendations are only applicable for new drugs; therefore, it will be the duty of all our colleagues, all around the word, to perform such studies on ESRD patients.

Funding

This paper was not funded.

Declaration of interest

N. Janus has the following indirect conflicts of interest (grants, institutional support, etc.): Bayer, Daiichi-Sankyo, Gilead, Ipsen, Leo Pharma, Pierre Fabre Oncology, Roche, Teva. N. Janus has the following direct conflicts of interest (Honoraria): Leo Pharma, Pfizer, Roche.

V. Launay-Vacher has the following indirect conflicts of interest (grants, institutional support, etc.): Bayer, Boehringer-Ingelheim, Daiichi-Sankyo, Gilead, Helsinn, Hospira, Ipsen, Leo Pharma, Pierre Fabre Oncology, Roche, Teva. V. Launay-Vacher has the following direct conflicts of interest (Honoraria/advisor): Amgen, Leo Pharma, Pierre Fabre Oncology, Merck, Roche, Takeda, Teva.

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Maisonneuve P, Agodoa L, Gellert R, et al. Cancer in patients on dialysis for end-stage renal disease: an international collaborative study. Lancet. 1999 juill 10;354(9173):93-9.
   - • **One of the very first papers that provided key epidemiologic data about cancer and the kidney.**
2. Vajdic CM, McDonald SP, McCredie MRE, et al. Cancer incidence before and after kidney transplantation. Jama. 2006 déc 20;296(23):2823-31.
3. Cucković C, Djukanović L, Janković S, et al. Malignant tumors in haemodialysis patients. Nephron. 1996;73(4):710-2.
4. Matas AJ, Simmons RL, Kjellstrand CM, et al. Increased incidence of malignancy during chronic renal failure. Lancet. 1975 avr 19;1 (7912):883-6.
5. Sutherland GA, Glass J, Gabriel R. Increased incidence of malignancy in chronic renal failure. Nephron. 1977;18(3):182–184.
6. Cengiz K. Increased incidence of neoplasia in chronic renal failure (20-year experience). Int Urol Nephrol. 2002;33(1):121-6.
7. Stengel B. Chronic kidney disease and cancer: a troubling connection. J Nephrol. 2010 juin;23(3):253-62.
   - •• **One of the very best papers about the link between cancer and renal function.**
8. Vogelzang JL, Van Stralen KJ, Noordzij M, et al. Mortality from infections and malignancies in patients treated with renal replacement therapy: data from the ERA-EDTA registry. Nephrol Dial Transplant. 2015 juin;30(6):1028-37.
9. Cheung CY, Chan GCW, Chan SK, et al. Cancer incidence and mortality in chronic dialysis population: a multicenter cohort study. Am J Nephrol. 2016;43(3):153-9.
10. Mandayam S, Shahinian VB. Are chronic dialysis patients at increased risk for cancer? J Nephrol. 2008 avr;21(2):166-74.
11. Janus N, Launay-Vacher V, Thyss A, et al. Management of anticancer treatment in patients under chronic dialysis: results of the multicentric CANDY (CANcer and DialYsis) study. Ann Oncol. 2013 févr;24(2):501–507.
12. Verbeeck RK, Musuamba FT. Pharmacokinetics and dosage adjustment in patients with renal dysfunction. Eur J Clin Pharmacol. 2009 août;65(8):757–773..
   - •• **One of the most recent and complete review about the pharmacokinetic modifications in CKD patients**
13. Hollander D. Intestinal permeability, leaky gut, and intestinal disorders. Curr Gastroenterol Rep. 1999 oct;1(5):410–416.
14. Ryss ES, Lutoshkin MB. Changes in the large intestine in patients with chronic kidney failure. Ter Arkh. 1996;68(6):33-7.
15. Leblond FA, Petrucci M, Dubé P, et al. Downregulation of intestinal cytochrome p450 in chronic renal failure. J Am Soc Nephrol. 2002 juin;13(6):1579–1585.
16. Gibson TP. Renal disease and drug metabolism: an overview. Am J Kidney Dis. 1986 juill;8(1):7-17.
17. Khosravan R, Toh M, Garrett M, et al. Pharmacokinetics and safety of sunitinib malate in subjects with impaired renal function. J Clin Pharmacol. 2010 avr;50(4):472–481.
18. Bowmer CJ, Lindup WE. Decreased drug binding in uraemia: effect of indoxyl sulphate and other endogenous substances on the binding of drugs and dyes to human albumin. Biochem Pharmacol. 1982 févr 1;31(3):319-23.
19. Launay-Vacher V, Storme T, Izzedine H, et al. Pharmacokinetic changes in renal failure. Presse Med. 2001 mars 31; 30(12):597-604..
   - • **One of the first reviews about the pharmacokinetic modifications in CKD patients**
20. de Jongh FE, Van Veen RN, Veltman SJ, et al. Weekly high-dose cisplatin is a feasible treatment option: analysis on prognostic factors for toxicity in 400 patients. Br J Cancer. 2003 avr 22;88 (8):1199–1206.
21. Arrieta O, Michel Ortega RM, Villanueva-Rodríguez G, et al. Association of nutritional status and serum albumin levels with development of toxicity in patients with advanced non-small cell lung cancer treated with paclitaxel-cisplatin chemotherapy: a prospective study. BMC Cancer. 2010;10:50.
22. Fujita K, Masuo Y, Okumura H, et al. Increased plasma concentrations of unbound SN-38, the active metabolite of irinotecan, in cancer patients with severe renal failure. Pharm Res. 2016 févr;33 (2):269–282.
23. Lam YW, Banerji S, Hatfield C, et al. Principles of drug administration in renal insufficiency. Clin Pharmacokinet. 1997 janv;32(1):30-57.
24. Weil A, Martin P, Smith R, et al. Pharmacokinetics of vandetanib in subjects with renal or hepatic impairment. Clin Pharmacokinet. 2010 sept;49(9):607–618.
25. Martin P, Oliver S, Kennedy S-J, et al. Pharmacokinetics of vandetanib: three phase I studies in healthy subjects. Clin Ther. 2012 janv;34(1):221–237.
26. Sun H, Huang Y, Frassetto L, et al. Effects of uraemic toxins on hepatic uptake and metabolism of erythromycin. Drug Metab Dispos. 2004 nov;32(11):1239-46.
27. Sun H, Frassetto L, Benet LZ. Effects of renal failure on drug transport and metabolism. Pharmacol Ther. 2006 janv;109(1–2):1–11.

28. Iyer L, Ratain MJ. 5-fluorouracil pharmacokinetics: causes for variability and strategies for modulation in cancer chemotherapy. Cancer Invest. 1999;17(7):494-506.
29. Janus N, Thariat J, Boulanger H, et al. Proposal for dosage adjustment and timing of chemotherapy in hemodialyzed patients. Ann Oncol. 2010 juill;21(7):1395–1403.
30. Poole C, Gardiner J, Twelves C, et al. Effect of renal impairment on the pharmacokinetics and tolerability of capecitabine (Xeloda) in cancer patients. Cancer Chemother Pharmacol. 2002 mars;49(3):225-34.
31. Prestayko AW, D'Aoust JC, Issell BF, et al. Cisplatin (cis-diamminedichloroplatinum II). Cancer Treat Rev. 1979 mars;6(1):17-39.
32. Tanabe N, Goto M, Morita H, et al. Pharmacokinetics of cis-diammine-dichlor-platin in a haemodialysis patient. Cancer Invest. 1991;9(6):629–635.
33. Gorodetsky R, Vexler A, Bar-Khaim Y, et al. Plasma platinum elimination in a haemodialysis patient treated with cisplatin. Ther Drug Monit. 1995 avr;17(2):203–206.
34. Kurisu A, Hata T, Owada A. Full-dose chemotherapy for esophageal cancer patient under haemodialysis. Nephron. 2002 déc;92(4):960.
35. Watanabe R, Takiguchi Y, Moriya T, et al. Feasibility of combination chemotherapy with cisplatin and etoposide for haemodialysis patients with lung cancer. Br J Cancer. 2003 janv 13;88(1):25-30.
36. Naud J, Michaud J, Boisvert C, et al. Down-regulation of intestinal drug transporters in chronic renal failure in rats. J Pharmacol Exp Ther. 2007 mars;320(3):978-85.
37. Naud J, Michaud J, Beauchemin S, et al. Effects of chronic renal failure on kidney drug transporters and cytochrome P450 in rats. Drug Metab Dispos. 2011 août;39(8):1363-9.
38. Abbruzzese JL, Grunewald R, Weeks EA, et al. A phase I clinical, plasma, and cellular pharmacology study of gemcitabine. J Clin Oncol. 1991 mars;9(3):491-8.
39. Masumori N, Kunishima Y, Hirobe M, et al. Measurement of plasma concentration of gemcitabine and its metabolite dFdU in haemodialysis patients with advanced urothelial cancer. Jpn J Clin Oncol. 2008 mars;38(3):182–185.
40. Kiani A, Köhne C-H, Franz T, et al. Pharmacokinetics of gemcitabine in a patient with end-stage renal disease: effective clearance of its main metabolite by standard haemodialysis treatment. Cancer Chemother Pharmacol. 2003 mars;51(3):266-70.
41. Lichtman SM, Wildiers H, Launay-Vacher V, et al. International Society of Geriatric Oncology (SIOG) recommendations for the adjustment of dosing in elderly cancer patients with renal insufficiency. Eur J Cancer. 2007 janv;43(1):14-34.
42. Kasichayanula S, Liu X, Pe Benito M, et al. The influence of kidney function on dapagliflozin exposure, metabolism and pharmacodynamics in healthy subjects and in patients with type 2 diabetes mellitus. Br J Clin Pharmacol. 2013 sept;76(3):432-44.
43. Janus N, Launay-Vacher V, Karie S, et al. Vaccination and chronic kidney disease. Nephrol Dial Transplant. 2008 mars;23(3):800-7.
44. Johnson DW, Fleming SJ. The use of vaccines in renal failure. Clin Pharmacokinet. 1992 juin;22(6):434–446.
45. Mittendorf EA, Peoples GE. Injecting hope – a review of breast cancer vaccines. Oncology (Williston Park, NY). 2016 mai;30 (5):475–81, 485.
46. Launay-Vacher V. Epidemiology of chronic kidney disease in cancer patients: lessons from the IRMA study group. Semin Nephrol. 2010 nov;30(6):548–556..
    • **One of the best reviews about the impact of renal function on overall survival in cancer patients**
47. Nakamura Y, Tsuchiya K, Nitta K, et al. Prevalence of anemia and chronic kidney disease in cancer patients: clinical significance for 1-year mortality. Nihon Jinzo Gakkai Shi. 2011;53(1):38-45.
48. Iff S, Craig JC, Turner R, et al. Reduced estimated GFR and cancer mortality. Am J Kidney Dis. 2014 janv;63(1):23-30.
49. Chen J, Wang X-T, Luo P-H, et al. Effects of unidentified renal insufficiency on the safety and efficacy of chemotherapy for metastatic colorectal cancer patients: a prospective, observational study. Support Care Cancer. 2015 avr;23(4):1043–1048.
50. Lichtman SM, Cirrincione CT, Hurria A, et al. Effect of pretreatment renal function on treatment and clinical outcomes in the adjuvant treatment of older women with breast cancer: alliance A171201, an ancillary study of CALGB/CTSU 49907. J Clin Oncol. 2016 mars 1;34 (7):699–705.
51. van Leeuwen RWF, Brundel DHS, Neef C, et al. Prevalence of potential drug–drug interactions in cancer patients treated with oral anticancer drugs. Br J Cancer. 2013 févr;108(5):1071-8.
52. van Leeuwen RWF, Jansman FGA, van den Bemt PMLA, et al. Drug-drug interactions in patients treated for cancer: a prospective study on clinical interventions. Ann Oncol. 2015 mai;26(5):992-7.
53. Segal EM, Flood MR, Mancini RS, et al. Oral chemotherapy food and drug interactions: a comprehensive review of the literature. J Oncol Pract. 2014 juill;10(4):e255–268.
54. SiteGPR® [Internet]. Guide de prescription et rein. [cité 15 janv 2016]. Disponible sur: http://www.sitegpr.com
    •• **Website providing recommendations for the dose adjustment of all drugs in CKD patients.**