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COMMENTARY

Chemotherapy in patients with severely reduced glomerular filtration rate: challenges and a call for improvement

Sabine Karam[1,2] · Jolanta Małyszko[3] · Ben Sprangers[4,5] · Rafal Stec[6] · Mitchell Rosner[7]

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Introduction

Both cancer and chronic kidney disease (CKD) are major public health issues worldwide [1, 2]. By 2060 cancer is estimated to become the leading cause of mortality worldwide [3], while the global prevalence of CKD is estimated to be around 10% [4]. Of great importance is the intersection of these two common conditions. Epidemiological studies have shown that CKD is associated with a higher risk of cancer development [5–9]. In addition, both the incidence and prevalence of CKD are high in cancer patients, with 10–20% of cancer patients having an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73m^2. The bidirectional link between cancer and CKD is highlighted in Fig. 1. The combination of cancer and CKD, and particularly advanced CKD (stage 4 and 5), is predictive of early mortality [10]. Indeed, as kidney dysfunction has significant effects on the elimination and metabolism of anti-cancer drugs, patients with reduced kidney function are less likely to receive optimal anti-cancer therapy [10] and are typically excluded from clinical trials [11]. Compounding this issue is that CKD stage 5 patients on dialysis may have variable drug removal during their kidney replacement therapy (KRT) sessions, which may result in a loss of anti-tumor efficacy. Awareness of the potential pharmacokinetic and pharmacodynamic modifications that occur with anticancer drugs in patients with CKD may improve outcomes, especially in patients with GFR < 30 mL/min/1.73m^2. In this commentary, we detail the complex changes occurring in the pharmacokinetics and pharmacodynamics of drugs in CKD and provide general dosing guidance based upon these principles.

Changes in pharmacokinetics and pharmacodynamics in CKD patients

The effect of a drug is determined by both its pharmacokinetic and pharmacodynamic characteristics. A drug's pharmacokinetic properties are defined as absorption, distribution, metabolism, and excretion (ADME). While its pharmacodynamic properties are the consequence of its drug/receptor interaction, interactions with cellular targets, and downstream pathways. CKD affects both the pharmacokinetic and pharmacodynamic characteristics of cancer drugs in ways that are unexpected and not predictable (Fig. 2). Pharmacokinetic modifications in CKD include changes in absorption, bioavailability, protein-binding, volume of distribution, metabolism, and excretion, even if the drug is not primarily eliminated by renal mechanisms. Other parameters to also consider in CKD patients include expression of drug transporters and drug-drug interactions given the high prevalence of polypharmacy in this particular population [12]. With regard to orally administered drugs, altered gastrointestinal transit time, a modified gastric pH that affects ionization state, vomiting, diarrhea, and drug–drug interactions all constitute factors that can limit absorption [13]. In advanced CKD, gastric pH can increase due to ammonia formation in the gut, secondary

✉ Sabine Karam
skaram@umn.edu

1 Division of Nephrology and Hypertension, Department of Medicine, University of Minnesota, 717 Delaware Street SE, Minneapolis, MN 55414, USA

2 Division of Nephrology and Hypertension, Department of Internal Medicine, American University of Beirut, Beirut, Lebanon

3 Department of Nephrology, Dialysis and Internal Diseases, The Medical University of Warsaw, Warsaw, Poland

4 Ziekenhuis Oost-Limburg, Genk, Belgium

5 Department of Immunology, and Infection, Biomedical Research Institute, UHasselt, Diepenbeek, Belgium

6 Department of Oncology, The Medical University of Warsaw, Warsaw, Poland

7 Division of Nephrology, University of Virginia Health, Charlottesville, USA

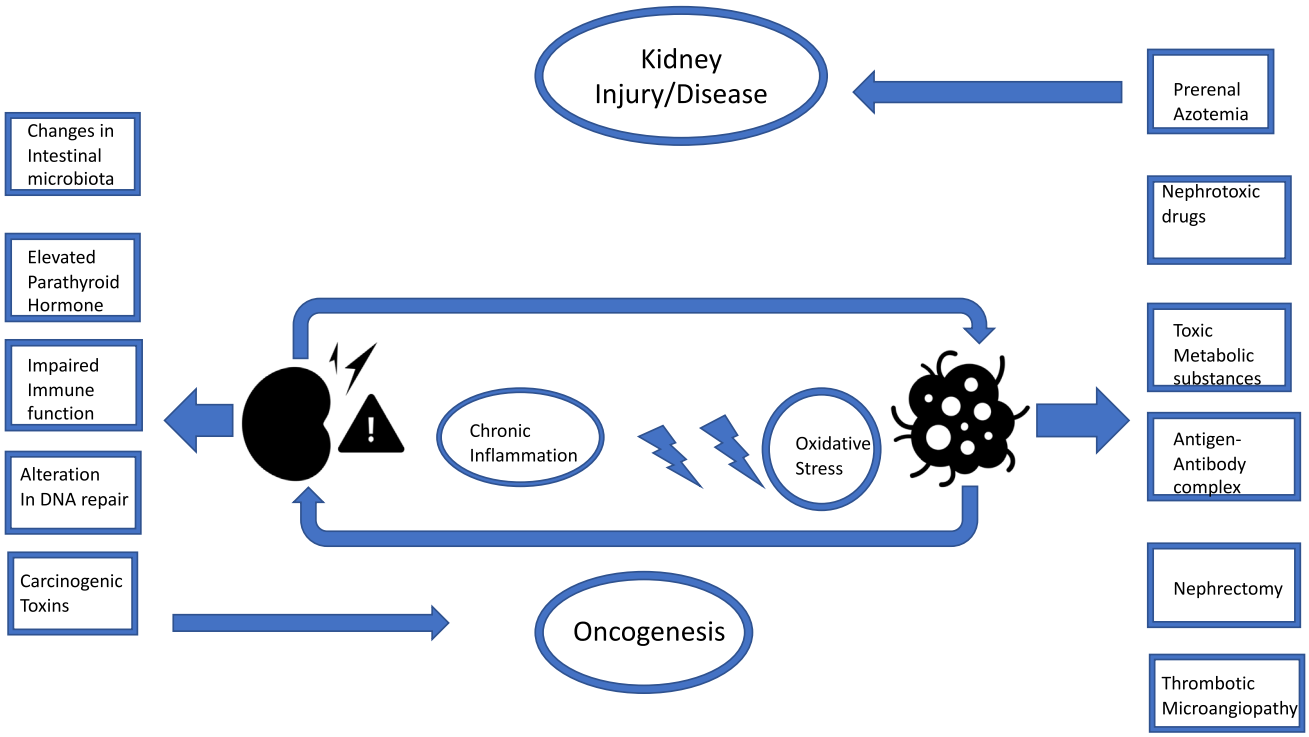

Fig. 1 CKD and Cancer Interaction

to conversion of salivary urea by urease enzymes [14], but it can also be altered by the extensive utilization of phosphate binders, H2-receptor antagonists, and proton-pump inhibitors in this patient population [15, 16]. Changes in the integrity of the intestinal wall can occur as well, secondary to decreased functional expression of intestinal cytochrome P and transporters [17], or because of inflammation leading to an increase in permeability [18]. Conversely, bowel edema, a common occurrence in CKD, can limit absorption [19–21]. In terms of bioavailability, alterations in body composition induced by CKD can lead to either an increase (due to hypoalbuminemia, decreased serum albumin binding, increased tissue binding or changes in body composition) or a decrease (due to sarcopenia) in the volume of distribution (Vd) of a chemotherapeutic drug [13]. Protein-binding can also be an issue as uremic toxins can compete with drugs for plasma protein-binding sites, leading to altered pharmacokinetics. In patients with hypoalbuminemia (due to nephrotic syndrome or poor nutritional status), the free fraction of some drugs may be increased, with subsequent altered kinetics and actions. For example, development of toxicity has been observed in patients with lung cancer who have malnutrition and low albumin levels receiving cisplatin plus paclitaxel chemotherapy [22]. With regard to drugs that are not renally excreted, kidney impairment can influence the hepatic metabolism of some of these drugs by modifying cytochrome P enzyme activity and transporter functions [23]. Hepatically metabolized drugs are more susceptible to first-pass metabolism, which can be altered in CKD and could potentially result in decreased serum concentration of a drug [24]. Another important aspect to consider when biliary excretion of hepatically metabolized compounds of drugs occurs, is that some metabolites can potentially be reabsorbed in a process known as enterohepatic cycling, and may ultimately need to be eliminated through the urine [25]. These metabolites may have biological activity and/or toxicity. An example of this is the metabolism and excretion of morphine [26]. To highlight the effects of CKD on nonrenal mechanisms of drug handling, a Food and Drug Administration (FDA) survey of new drug applications found that approximately 25% of compounds not primarily eliminated via the kidney demonstrated a twofold or greater increase in plasma concentration of the area under the curve (AUC) in patients with kidney dysfunction [27]. Rosuvastatin, a cholesterol-lowering agent, is one such example. Although only 6% of rosuvastatin is eliminated via urine, plasma concentrations were reported to be increased threefold in patients with severe renal impairment, requiring dose adjustment [27]. Other examples of CKD interacting with non-renal drug handling include a lower absorption rate of sunitinib in patients with reduced kidney function compared to patients with normal function [28].

Nonetheless, there remains limited pharmacokinetic/pharmacodynamic data for chemotherapeutic drugs in

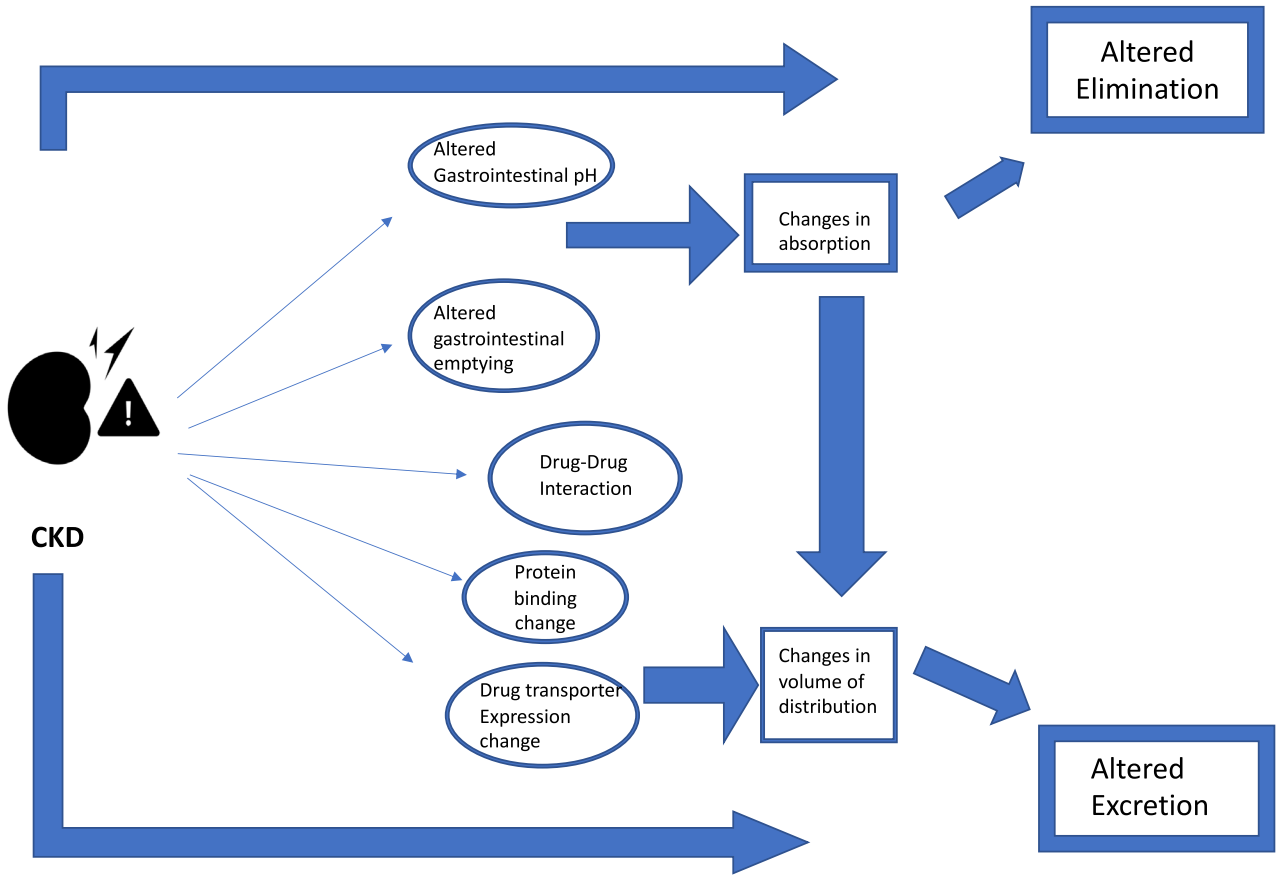

Fig. 2 Alterations of pharmacokinetics and pharmacodynamics of drugs in CKD

patients with CKD. Dialytic therapies add another level of complexity, especially in stage 4 and 5 patients. For example, patients with severe kidney dysfunction without dialysis have a $a > 50\%$ reduction in lidocaine clearance, while no significant change in lidocaine elimination was found in dialysis patients compared to healthy controls [29]. The dialysis procedure may remove certain drugs, and thus require dose adjustment or supplementation for these agents. And while data is scarce regarding drug elimination and dosing in patients on hemodialysis, it is even scarcer for patients on peritoneal dialysis (PD), a population on the rise worldwide.

Both the FDA and the European Medicines Agency (EMA) have published guidance documents for industry with requirements for pharmacokinetic studies in patients with impaired GFR [30]. The FDA also recommends that pharmacokinetic studies in kidney impairment models be conducted for medications that are not renally eliminated. Ultimately, the goal of a pharmacokinetic renal impairment study is to estimate the impact of varying degrees of renal impairment on the systemic availability (as typically measured by AUC and maximal plasma concentration [C_{max}]) of the drug and/or relevant metabolites [30]. This assessment includes drugs handled directly by kidney clearance as well as by indirect effects. Where significant alterations in AUC and C_{max} are detected, a recommendation for dose adjustment may be necessary in one or more stages of renal impairment irrespective of the degree of renal clearance.

General principles of drug dosing in CKD

The first step in kidney function-adjusted drug dosing is the determination of kidney function, typically done through measured or estimated GFR using a regression equation. The method used to measure/estimate kidney function is dependent on the accuracy needed to allow clinical decision-making in a specific cancer patient considering the drug's risk/benefit (greater risk for toxicity can be tolerated in a patient in a rare curative scenario compared to more common palliative scenarios when only moderate anti-cancer effects are expected). When dealing with highly toxic and predominantly renally eliminated anticancer drugs with a narrow therapeutic index, direct measurement of GFR should be considered prior to prescribing the dose. This is especially true in advanced CKD and in AKI where the common equations used to estimate kidney function perform

poorly. In general, dose adjustment is unlikely to be required when < 30% of a drug or its metabolites are eliminated by the kidneys, but as stated above, this may not always be the case and caution is warranted. Also, highly protein-bound drugs (> 80%) are in general not removed by the kidney or KRT. Finally, for a drug with a high Vd only a proportion of the drug is present in the plasma, and removal by renal excretion is limited [31]. Newer, targeted drugs (such as tyrosine kinase inhibitors or drugs targeting the vascular endothelial growth factor pathway) are generally not cleared by the kidney and therefore their dose does not need to be adjusted according to kidney function. Also, the primary route of elimination for monoclonal antibodies is not renal, but intracellular catabolism by lysosomal degradation following pinocytosis or receptor-mediated endocytosis. Consequently, no dose-adjustment is needed in patients with kidney dysfunction [32].

In patients with CKD stage 5D undergoing intermittent hemodialysis (iHD), clearance due to iHD should be considered additive to endogenous clearance and is highly dependent on the drug and dialysis characteristics. The impact of iHD on the drug's pharmacokinetic/pharmacodynamic characteristics depends on dialysis prescription (including dialysis filter, filter surface area, blood/dialysate/ultrafiltration rate and dialysis modality) and drug characteristics (molecular weight, protein binding, V_d). Different dialysis filters can result in different pharmacokinetic/pharmacodynamic results as certain drugs bind to the dialyzer membrane and various dialyzers have different molecular weight cutoffs for removal. There is some evidence that non-renal clearance can be altered in HD patients by a temporary increase in drug clearance following an HD session due to a transient decrease in uremic toxins inhibiting the enzyme *CYP450* 3A4 and drug transporters, resulting in a non-sustained increase in drug clearance. Peritoneal dialysis mainly results in clearance of small size molecules with a urea clearance of 10 mL/min and by extrapolation to drugs, in general their total clearance is only minimally affected, especially since most drug molecules are larger than urea [33]. Therefore, drug dosing recommendations for patients with eGFR < 15 ml/min are likely clinically applicable to PD patients as well.

Conclusions and recommendations

Unfortunately, for many available anticancer drugs, data concerning appropriate dosing in advanced CKD are lacking [34]. During drug development phases, initial clinical studies only include patients with normal or only mildly decreased kidney function. In subsequent preregistration studies, only a limited number of patients with more severe kidney dysfunction are included, typically with the exclusion of patients with CKD stage 5 and 5D before drug registration. This lack of data, in combination with other safety concerns, often results in a manufacturer stating that a drug is contraindicated in patients with advanced CKD. This limits the ability of these patients to benefit from potentially curative therapy.

It is time for a change! A comprehensive approach from both the oncology and the nephrology community and collaboration with industry is needed to address this gap and to establish accurate dosing recommendations for patients with kidney dysfunction, especially in stages 4 and 5 CKD. A starting point would be a mandate from the FDA and EMA to require studies of drugs at all stages of CKD as part of the approval process for new medications. In addition, research foundations should prioritize grants to better understand the myriad effects of advanced CKD on issues such a drug absorption, volume of distribution, drug-drug interactions, and elimination kinetics of drugs. For those drugs impacted by CKD, information on availability of drug levels and correlation with therapeutic and toxic effects would allow for more personalized approaches. Through these processes, a greater understanding of the interactions between CKD and cancer outcomes can be developed in an effort to improve outcomes and survival.

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Declarations

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References

1. Siegel RL, Miller KD, Fuchs HE, Jemal A (2022) Cancer statistics, 2022. CA Cancer J Clin 72:7–33. https://doi.org/10.3322/caac.21708
2. de Francisco ALM, Macía M, Alonso F et al (2019) Onco-nephrology: cancer, chemotherapy and kidney. Nefrologia (Engl Ed) 39:473–481. https://doi.org/10.1016/j.nefroe.2018.10.016
3. Mattiuzzi C, Lippi G (2019) Current cancer epidemiology. J Epidemiol Glob Health 9:217–222. https://doi.org/10.2991/jegh.k.191008.001
4. GBD Chronic Kidney Disease Collaboration (2020) Global, regional, and national burden of chronic kidney disease, 1990–2017: a systematic analysis for the global burden of disease study 2017. Lancet 395:709–733. https://doi.org/10.1016/S0140-6736(20)30045-3

5. Xu H, Matsushita K, Su G et al (2019) Estimated glomerular filtration rate and the risk of cancer. Clin J Am Soc Nephrol 14:530–539. https://doi.org/10.2215/CJN.10820918
6. Lowrance WT, Ordoñez J, Udaltsova N et al (2014) CKD and the risk of incident cancer. J Am Soc Nephrol 25:2327–2334. https://doi.org/10.1681/ASN.2013060604
7. Wong G, Hayen A, Chapman JR et al (2009) Association of CKD and cancer risk in older people. J Am Soc Nephrol 20:1341–1350. https://doi.org/10.1681/ASN.2008090998
8. Miyamoto Y, Katagiri R, Yamaji T et al (2022) Association of chronic kidney disease with total and site-specific cancer incidence in participants of the Japan public health center-based prospective study. Nephrol Dial Transplant 38:1487–1496. https://doi.org/10.1093/ndt/gfac288
9. Mok Y, Ballew SH, Sang Y et al (2020) Albuminuria, kidney function, and cancer risk in the community. Am J Epidemiol 189:942–950. https://doi.org/10.1093/aje/kwaa043
10. Chen X, Li Y, Ding X et al (2020) Incidence, risk, and prognosis of cancer in patients on chronic hemodialysis. Blood Purif 49:310–321. https://doi.org/10.1159/000504243
11. Janus N, Launay-Vacher V, Thyss A et al (2013) Management of anticancer treatment in patients under chronic dialysis: results of the multicentric CANDY (CANcer and DialYsis) study. Ann Oncol 24:501–507. https://doi.org/10.1093/annonc/mds344
12. Janus N, Launay-Vacher V (2017) Pharmacokinetic/pharmacodynamic considerations for cancer patients undergoing hemodialysis. Expert Opin Drug Metab Toxicol 13:617–623. https://doi.org/10.1080/17425255.2017.1292252
13. Campoy S, Elwell R (2005) Pharmacology & CKD: how chronic kidney disease and its complications alter drug response. Am J Nurs 105:60–71. https://doi.org/10.1097/00000446-200509000-00029
14. St Peter WL, Redic-Kill KA, Halstenson CE (1992) Clinical pharmacokinetics of antibiotics patients with impaired renal function. Clin Pharmacokinet 22:169–210. https://doi.org/10.2165/00003088-199222030-00002
15. Nolin TD, Frye RF, Matzke GR (2003) Hepatic drug metabolism and transport in patients with kidney disease. Am J Kidney Dis 42:906–925. https://doi.org/10.1016/j.ajkd.2003.07.019
16. Gugler R, Allgayer H (1990) Effects of antacids on the clinical pharmacokinetics of drugs. An update. Clin Pharmacokinet 18:210–219. https://doi.org/10.2165/00003088-199018030-00003
17. Naud J, Nolin TD, Leblond FA, Pichette V (2012) Current understanding of drug disposition in kidney disease. J Clin Pharmacol 52:10S–22S. https://doi.org/10.1177/0091270011413588
18. Hollander D (1999) Intestinal permeability, leaky gut, and intestinal disorders. Curr Gastroenterol Rep 1:410–416. https://doi.org/10.1007/s11894-999-0023-5
19. Swan SK, Bennett WM (1992) Drug dosing guidelines in patients with renal failure. West J Med 156:633–638
20. Talbert RL (1994) Drug dosing in renal insufficiency. J Clin Pharmacol 34:99–110. https://doi.org/10.1002/j.1552-4604.1994.tb03973.x
21. Lam YW, Banerji S, Hatfield C, Talbert RL (1997) Principles of drug administration in renal insufficiency. Clin Pharmacokinet 32:30–57. https://doi.org/10.2165/00003088-199732010-00002
22. Arrieta O, Michel Ortega RM, Villanueva-Rodríguez G et al (2010) 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 10:50. https://doi.org/10.1186/1471-2407-10-50
23. Yeung CK, Shen DD, Thummel KE, Himmelfarb J (2014) Effects of chronic kidney disease and uremia on hepatic drug metabolism and transport. Kidney Int 85:522–528. https://doi.org/10.1038/ki.2013.399
24. Gabardi S, Abramson S (2005) Drug dosing in chronic kidney disease. Med Clin North Am 89:649–687. https://doi.org/10.1016/j.mcna.2004.11.007
25. Ibarra M, Troconiz IF, Fagiolino P (2021) Enteric reabsorption processes and their impact on drug pharmacokinetics. Sci Rep 11:5794. https://doi.org/10.1038/s41598-021-85174-w
26. Hanks GW, Wand PJ (1989) Enterohepatic circulation of opioid drugs. Is it clinically relevant in the treatment of cancer patients? Clin Pharmacokinet 17:65–68. https://doi.org/10.2165/00003088-198917020-00001
27. Zhang Y, Zhang L, Abraham S et al (2009) Assessment of the impact of renal impairment on systemic exposure of new molecular entities: evaluation of recent new drug applications. Clin Pharmacol Ther 85:305–311. https://doi.org/10.1038/clpt.2008.208
28. Khosravan R, Toh M, Garrett M et al (2010) Pharmacokinetics and safety of sunitinib malate in subjects with impaired renal function. J Clin Pharmacol 50:472–481. https://doi.org/10.1177/0091270009347868
29. De Martin S, Orlando R, Bertoli M et al (2006) Differential effect of chronic renal failure on the pharmacokinetics of lidocaine in patients receiving and not receiving hemodialysis. Clin Pharmacol Ther 80:597–606. https://doi.org/10.1016/j.clpt.2006.08.020
30. Paglialunga S, Offman E, Ichhpurani N et al (2017) Update and trends on pharmacokinetic studies in patients with impaired renal function: practical insight into application of the FDA and EMA guidelines. Expert Rev Clin Pharmacol 10:273–283. https://doi.org/10.1080/17512433.2017.1274651
31. Fagugli RM, De Smet R, Buoncristiani U et al (2002) Behavior of non-protein-bound and protein-bound uremic solutes during daily hemodialysis. Am J Kidney Dis 40:339–347. https://doi.org/10.1053/ajkd.2002.34518
32. Kitchlu A, Jhaveri KD, Sprangers B et al (2021) Immune checkpoint inhibitor use in patients with end-stage kidney disease: an analysis of reported cases and literature review. Clin Kidney J 14:2012–2022. https://doi.org/10.1093/ckj/sfab090
33. Paton TW, Cornish WR, Manuel MA, Hardy BG (1985) Drug therapy in patients undergoing peritoneal dialysis. Clinical pharmacokinetic considerations. Clin Pharmacokinet 10:404–425. https://doi.org/10.2165/00003088-198510050-00003
34. Major R, Selvaskandan H, Makkeyah YM et al (2020) The exclusion of patients with CKD in prospectively registered interventional trials for COVID-19-a rapid review of international registry data. J Am Soc Nephrol 31:2250–2252. https://doi.org/10.1681/ASN.2020060877