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REVIEW

# Improving Cancer Care for Patients With CKD: The Need for Changes in Clinical Trials



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Chemotherapeutic agents used to treat cancer generally have narrow therapeutic indices along with potentially serious adverse toxicities. Many cancer drugs are at least partially excreted through the kidney and, thus, the availability of accurate data on safe and effective dosing of these drugs in patients with chronic kidney disease (CKD) is essential to guide treatment decisions. Typically, during drug development, initial clinical studies only include patients with normal or only mildly impaired kidney function. In subsequent preregistration studies, a limited number of patients with more severe kidney dysfunction are included. Data obtained from patients with either severe kidney dysfunction (here defined as an estimated glomerular filtration rate [eGFR] $<$ 30 ml/min or stage 4G CKD) or end-stage kidney disease (ESKD) requiring kidney replacement treatment are particularly limited before drug registration and only a minority of new drug applications to the US Food and Drug Administration (FDA) include data from this population. Unfortunately, limited data and/or other safety concerns may result in a manufacturer statement that the drug is contraindicated in patients with advanced kidney disease, which hinders access to potentially beneficial drugs for these patients. This systemic exclusion of patients with CKD from cancer drug trials remains an unsolved problem, which prevents provision of optimal clinical care for these patients, raises questions of inclusion, diversity, and equity. In addition, with the aging of the population, there are increasing numbers of patients with CKD and cancer who face these issues. In this review, we evaluate the scientific basis to exclude patients with CKD from cancer trials and propose a comprehensive strategy to address this problem.

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Studies estimate that approximately 50% of patients with cancer have decreased kidney function and receive at least 1 anticancer drug that requires dose adjustment due to variable levels of clearance by the kidneys.[1–3] For those drugs excreted by the kidney, a precise understanding of kidney function is needed to ensure achievement of therapeutic levels and avoidance of adverse events. Unfortunately, many anticancer drugs lack data on appropriate dosing when kidney function is impaired because patients with advanced kidney disease are excluded from most clinical trials.[4,5] In a study by Kitchlu *et al.*[6] evaluating 310 trials on anticancer agents that included 282,889 patients, 264 (85%) of clinical drug trials for the 5 most common malignancies published in high-impact factor journals excluded the vast majority of patients with kidney dysfunction. Remarkably, serum creatinine threshold values and not glomerular filtration rates (GFRs) were the exclusion criteria in 62% of patients.[6] Owing to the fact that kidney dysfunction is common in cancer patients, excluding these patients hampers data collection on potential adverse drug effects in this population and limits the access to cancer therapies that could potentially improve outcomes for patients with kidney dysfunction.[7] Often, patients with CKD are excluded from clinical trials that evaluate therapy without any kidney clearance or significant likelihood of nephrotoxicity (e.g., immunotherapies and hormonal therapies). These types of therapies often represent important potential alternatives to renally cleared and

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established nephrotoxic chemotherapies. Lack of data on the use of these therapies in patients with CKD further hampers access to potential beneficial anticancer treatment.

Importantly, it is well established that CKD is characterized by strong ethnic, socio-economic and racial disparities. In addition to the paucity of randomized clinical trials in nephrology, the most recent high-impact nephrology clinical trials reported relatively low enrollment of non-White populations,[8–11] despite the fact that non-White racial groups are at higher risk for kidney disease and associated comorbidities.[12–14] As a consequence, addressing the systemic exclusion of CKD patients from clinical trials will improve diversity and inclusiveness of clinical trials.[15]

## Why are Patients With CKD Excluded From Clinical Trials?

Patients with CKD pose a special challenge for oncology trials and sponsors may have concerns about supporting oncological trials involving patients with CKD, particularly those with advanced disease, because this could potentially skew their efficacy and safety results, and affect regulatory approval and product labeling. Of note, a similar situation exists in cardiovascular disease trials with patients with CKD.[16] Whereas, exclusion of patients with kidney dysfunction may be appropriate in certain settings such as in phase I trials when the metabolism and excretion of drugs may not be known, systematic exclusion of these patients in late phase clinical trials should be avoided.

Broadly, 3 challenges face patients with CKD when they are considered for enrollment in oncology trials. These challenges include the following: (i) trial sponsor concerns (ii) study design and implementation, and (iii) lack of robust trial infrastructure in nephrology.

## Trial Sponsor Concerns

Clinical trials are time consuming, expensive, and often burdensome on patients. The common reasons why trials fail include the following: failure to demonstrate safety and efficacy, prohibitive costs to develop the drug, inability to find and enroll patients who meet eligibility criteria, and underpowered trials that fail to meet statistical significance for their end points.[17] Given that CKD can add significant concern for accurate dosing and potentially increase the risks of adverse effects of chemotherapy agents, excluding patients with kidney function in the range of a GFR of $<60$ ml/min is standard in most clinical trials. Of note, in the study of Kitchlu *et al.*,[6] serum creatinine threshold values, not eGFR, were most commonly used as exclusion criteria for patients entering cancer clinical trials.

## Study Design and Implementation

Safety concerns are viewed as a major barrier to including patients with advanced CKD in cancer trials. Patients with CKD suffer from multiple comorbidities and take multiple medications, which places them at risk for adverse events and drug-drug interactions. Patients may be excluded from trial participation due to concerns that the intervention could worsen their CKD or cause adverse effects. Some of the solutions to improve this would be to develop the following strategies to mitigate safety concern: utilize novel study designs, prohibit or restrict medications that interact with study drug, understand the effect of investigational product on eGFR and or serum creatinine, and manage risks of exacerbating complication of CKD progression and/or electrolyte disorders. These complications are potentially manageable but require collaboration between nephrology and oncology providers.

Some end points used in the general population may not be relevant for patients with CKD and ESKD, and competing comorbidities may complicate analysis of trial results.[18] Funakoshi *et al.*[19] in a retrospective study of 675 patients, reported that hemodialysis patients had a high mortality rate due to causes other than cancer compared with nondialyzed patients. The CANDY (CANcer and DialYsis) multicenter study studied anticancer treatment in patients on long-term hemodialysis. This study reported that 88% of the patients required specific management of the cytotoxic drug; 44% developed iatrogenic toxicity in relation to inappropriate dose adjustment due to the lack of management recommendations in this specific group of patients; and inappropriate high dosing of chemotherapy drugs was more often associated with hematological, gastric and neurologic side effects.[20] As kidney excretion plays an important role in the elimination of anticancer agents, kidney failure can lead to drug accumulation, which increases toxicity. Solutions to combat this could include approaches such as allowing sponsors to have the option to enroll patients with CKD and/or ESKD, but exclude them in their key efficacy analysis that is presented to the FDA. Conducting a parallel trial for patients with CKD and/or ESKD (phase 3 CKD) for major cancer drugs may be another viable option. Alternatively, in patients with CKD and/or ESKD, cancer-specific end points should be considered (cancer-specific mortality instead of overall mortality). Finally, including nephrologists and patients with CKD in the development of such trial protocols early may be of an advantage.

The presence of kidney dysfunction might also be incompatible with imaging studies applied in clinical cancer trials because the assumption is that patients

with CKD are unable to safely undergo diagnostic studies with either iodinated contrast or gadolinium-based contrast. Because these clinical trials often require contrast-based radiologic evaluation to assess tumor burden and response, eliminating patients with CKD from these studies due to concerns about contrast-associated toxicity such as acute kidney injury (AKI) with iodinated contrast agents and nephrogenic systemic fibrosis (NSF) with gadolinium-based contrast media (GBCM) is an automatic exclusion criterion from the clinical trial. Though this seems to be a logical exclusion criterion for such clinical trials that assess drug efficacy and toxicity, the real question relates to whether patients with CKD are truly at significant risk for the presumed toxicity from these agents. Importantly, the risk of toxicity is not the same for all levels of CKD.[21–24] Yet, patients with stage 3 CKD (eGFR <60 ml/min per 1.73 $m^2$) and higher are all considered to have similar risk. Furthermore, the risk for nephrotoxicity with i.v. contrast employed with computed tomography scans is lower as compared with arterial contrast injections.[21–24] The same applies to GBCM where the type of gadolinium chelate and contrast dose importantly drive risk for NSF in patients with CKD. The occurrence of NSF is very rare with newer GBCM (group II agents).[25–28] Ultimately, exclusion of CKD patients from indicated contrast-based diagnostic studies perpetuates a needless clinical paradigm not supported by clinical results or experience.

In first focusing on i.v. contrast computed tomography studies, the reality is that the nephrology community has played a significant role in pushing this very conservative approach by limiting contrast exposure in patients with CKD. Though iodinated contrast-associated AKI can occur in patients with eGFR <30 ml/min per 1.73 $m^2$, it is extremely uncommon in patients with CKD stages 1 to 3.[24] Consensus statements on i.v. contrast media use in patients with CKD were recently published by the American College of Radiology/National Kidney Foundation.[24] In their review of the literature, this group observed that the risk of contrast-associated AKI, which includes any AKI coincident to contrast media administration, increases as KDIGO CKD stage increases going from lower to higher stages.[24,29–34] At an eGFR ≥60 risk is ∼5%, which increases to 10% at eGFR of 45 to 59, 15% at eGFR of 30 to 44, and 30% at eGFR <30 ml/min per 1.73 $m^2$. This risk is higher than that seen for contrast-induced AKI, which implies a causal relationship between contrast media and the development of AKI.[24] Whereas the actual risk of contrast-induced AKI risk is uncertain in patients with advanced CKD, large, controlled, observational studies have shown little or no evidence of contrast-induced AKI, regardless of CKD stage.[24,29–34] In these studies, the risk of contrast-induced AKI is estimated to approximate 0% at eGFR ≥45, 0% to 2% at eGFR of 30 to 44, and 0% to 17% at eGFR of <30 ml/min per 1.73 $m^2$.[31,32,34–37] Based on these data, we must rethink the exclusion of cancer patients with an eGFR >30 ml/min per 1.73 $m^2$ from i.v. contrast studies. The potential risk of contrast-associated or induced AKI is likely far outweighed by the benefit of participation in cancer trials.

Magnetic resonance imaging studies using GBCM enhancement in patients with AKI and CKD (eGFR <30 ml/min per 1.73 $m^2$) were shown to be complicated by NSF. This devastating illness was observed almost exclusively with gadolinium bound to linear chelates (group I), use of higher than recommended doses, and repeated dosing within short imaging intervals. As a result, GBCM was contraindicated for use in patients with AKI and an eGFR <30 ml/min per 1.73 $m^2$. This was associated with a dramatic reduction in NSF. Nevertheless, the risk for NSF is not the same for all of GBCM. Group II GBCM (macrocyclic chelates) appears to be safer than the group I agents. The difference may be explained by different kinetic labilities of linear nonionic (more labile) and macrocyclic (less labile) GBCM, and differences in pharmacologic properties among GBCM such as degree of hepatobiliary excretion and/or degree of protein-binding.[38] Consensus statements on GBCM in patients with kidney disease were recently published by the American College of Radiology/National Kidney Foundation.[25] In their review of the literature, they found that few unconfounded NSF cases were associated with group II GBCM. These include GBCM with macrocyclic chelates-gadoterate meglumine, gadobutrol, and gadoteridol. Gadobenate dimeglumine is a linear ionic chelate and ∼5% hepatobiliary excretion that is also included in Group II because evidence supports a very low risk of NSF as compared with macrocyclic GBCM.[25–28] In 405 patients diagnosed with NSF, group II GBCM exposures were reported in 23 patients; however, only 2 were unconfounded.[25,26,39,40] A systematic review and meta-analysis of 4931 group II GBCM administrations in patients with stage 4 or 5 CKD noted that the risk of NSF was 0% (0 cases in 4931 subjects; upper bound of the 95% CI: 0.07%).[28] Subanalysis of these data stratified by CKD stage found that in all patients with stage 5 or 5D CKD (on dialysis), the upper bound of the 95% CI of risk was 0.1% (1 case for every 1000 exposed patients) based on 0 cases in 2581 exposed individuals.[41] Analyses of these 2 groups separately found the upper bound of the 95% CI of risk to be 0.5% (1 case for every 200 exposed patients) for stage 5 CKD based on 0 cases in 732 exposed individuals, and 0.2% (1 case for every 500 exposed

patients) for stage 5D CKD based on 0 cases in 1849 exposed individuals.[41] Thus, as with i.v. contrast media, the use of GBCM in CKD patients must be reassessed. Administration of GBCM appears safe in patients with all stages of CKD including stage 5D.

To allow patients with advanced CKD to participate in these clinical trials, a reasonable approach would be to employ i.v. contrast studies in patients with an eGFR $>30$ ml/min per 1.73 $m^2$ and GBCM in patients with an eGFR $<30$ ml/min per 1.73 $m^2$. This approach needs to be factored in, along with choosing the appropriate diagnostic imaging technique for the cancer of interest. Therefore, the exclusion of CKD patients from clinical trials based on the avoidance of contrast-enhanced radiological studies is over-restrictive and not supported by the data.

## Lack of Robust Trial Infrastructure in Nephrology

Compared with cardiology and oncology trials, nephrology has the fewest randomized clinical trials[42,43] and the majority of existing trials lack adequate power to detect treatment effects that can be realistically achieved with one treatment intervention.[44] The design and conduct of kidney disease trials can be challenging for many reasons. Sample size and power calculations are underpinned by a number of assumptions, which may not hold true despite best estimates. Compared with the general population, medication dosing, tolerance to side effects, and adherence often differs in patients with CKD who have a high burden of illness and high rate of adverse events. In addition, recruitment for kidney disease trials is often challenging due to limitations in coordinated global trial networks and infrastructure. Many well-designed trials set out with good intentions, but are unsuccessful due to unanticipated challenges in recruitment, adherence, outcome rates, or other factors. There is little infrastructure, and few incentives for nephrologists to enroll their patients in clinical trials. An issue of particular concern in the United States is that enrollment of dialysis patients in cancer trials requires additional stakeholders such as large dialysis organizations to agree to trial participation. In the last 3 decades, there has been continued growth in the for-profit large dialysis organizations in the United States. Two large dialysis organizations in particular, Fresenius Medical Care and DaVita Healthcare Partners, Inc., are now dominant as providers of dialysis services in the United States, with nearly two-thirds of facilities; their industry dominance is also growing on the international level as $>80\%$ of dialysis patients receive their treatments from either DaVita Healthcare Partners, Inc. or Fresenius Medical Care. In contrast, there has been little to no growth in the provision of dialysis services by all other dialysis organizations that include not-for-profit organizations or hospital-based dialysis facilities, and all other smaller for-profit dialysis organizations. Partnerships with large dialysis organizations are therefore essential for the success of cancer trials in patients with ESKD. Overall, the trial culture in nephrology is still very immature.[45] Relevant specialty societies should partner and take the lead in encouraging junior investigators to take part in such trials and allow for increased funding.

## Understanding and Overcoming the Challenges Related to Oncological Trials Involving Patients With Kidney Disease

Patients should not be inappropriately excluded from trials if the effects of kidney dysfunction can be monitored and mitigated through appropriate dose modification.[46] The American Society of Clinical Oncology and Friends of Cancer Research have published recommendations regarding eligibly of patients with kidney dysfunction.[47] The recommendations are as follows:

1. Eligibility criteria should include assessment of creatinine clearance rather than serum creatinine concentrations.
2. The Cockcroft-Gault and MDRD equations are reasonable standards for calculating kidney function and are accepted in practice. A consistent measure should be applied throughout the drug development process. Inclusion of patients with renal dysfunction could be liberalized in the following specific settings: if renal toxicity and clearance are not of concern, then lower CrCl values of $>30$ ml/min should be used for inclusion; when published dose modifications allow for safe and effective administration of the drug and are not likely to change outcomes (e.g., carboplatin, methotrexate, capecitabine); and when the totality of the available nonclinical and clinical data, including pharmacokinetic and pharmacodynamic data, indicates that inclusion of patients with renal dysfunction is safe. Ideally, as nephrologists, we would prefer the CKD Epidemiology Collaboration (CKD-EPI) GFR equation over the Cockcroft-Gault and MDRD equations for kidney function estimations. However, we applaud the recommendation made by the American Society of Clinical Oncology and Friends of Cancer Research as implementation of this recommendation would stop the current practice of using serum creatinine as estimate of kidney function.

The FDA has used these guidelines as a basis for their Guidance Document: Cancer Clinical Trial Eligibility

Criteria: Patients with Organ Dysfunction or Prior or Concurrent Malignancies.[48] The Cancer Therapy Evaluation Program template for clinical trials also incorporates these recommendations.[49] The hope is to minimize the number of patients unnecessarily excluded.

## Precise Estimation of Kidney Function

In general, 2 pathways are involved in the excretion of drugs and their metabolites by the kidney: glomerular filtration and tubular secretion. Glomerular filtration is relevant for smaller, nonprotein-bound substances, while tubular secretion is a more common pathway for protein-bound compounds. In addition, tubular reabsorption of a drug can occur, which can raise the concentration of the drug. A recent study showed that in stable outpatients, there is strong linkage between GFR and tubular secretory clearance.[50] Therefore, although currently used formulas estimating kidney function mainly evaluate GFR and do not account for the contribution of tubular secretion to drug clearance (unless a drug has a secretion profile similar to that of creatinine), eGFR can be accepted as the best available measure of functioning kidney mass.[51] Measures to directly and indirectly measure GFR have been well validated and there is extensive experience with their operational characteristics, which makes their use ideal in design of clinical trials, determination of appropriate dosing guidelines for various levels of kidney function, and for the care of patients with cancer. Recognizing the fact that nonkidney clearance mechanisms can be altered in patients with impaired kidney function,[52] the US FDA has recommended that pharmacokinetic studies in kidney impairment models be conducted for medications that are not eliminated by the kidney.

Though many methodologies exist to measure GFR, many are not practical in daily clinical use.[53] Serum markers (such as creatinine and cystatin C) have been developed to be used in GFR estimating equations, whereas in some circumstances, more precise determination of GFR is needed and then urinary clearance of an ideal filtration marker can be utilized (typically through radionuclides and radiocontrast agents where clearance can be determined as the amount of indicator injected divided by the integrated area of plasma concentration curve over time).[54,55] Substances such as $^{125}$I-iothalamate and $^{51}$Cr-EDTA (detected by plasma levels) or $^{99}$m-Tc mercaptoacetyltriglycine (MAG3) and $^{99}$m-Tcdiethyl triamine penta-acetic acid (99mTc-DTPA) (detected by gamma counter) can be used for direct GFR measurement.[54,55] More typical and more practical is estimation of GFR through various regression equations that may include: creatinine clearance estimation, eGFR measurements, or cancer-specific equations that aim to take into consideration patient-specific factors impacting kidney function measurement. Though the National Comprehensive Cancer Network and the International Society of Geriatric Oncology recommend an assessment of kidney function before the administration of chemotherapeutic drugs, even in patients with "normal" kidney function, there are no collective guidelines declaring which method of estimating kidney function is preferred in patients with cancer.[56]

The CKD-EPI equation was developed to improve shortcomings of prior equations and is most commonly used in current clinical practice.[57] This equation utilizes serum creatinine values as well as age, sex and race to calculate an eGFR. There are also forms of the CKD-EPI equation that incorporate serum cystatin C to better refine GFR estimation.[58] Data suggests that 3.6% of US adults would be classified as having CKD solely on the basis of a creatinine-based GFR estimate of 45 to 59 ml/min per 1.73 $m^2$.[59] A strategy of measuring cystatin C when the creatinine-based estimate is in this range and then re-estimating GFR with the use of both these markers could correctly reclassify a substantial proportion of such patients as not having CKD and not being at high risk.[58,60] The CKD-EPI equation is currently recommended by the National Kidney Foundation-Kidney Disease Outcome Quality Initiative and the Kidney Disease Improving Global Outcomes guideline groups.[61] A point of recent controversy is that the CKD-EPI equation incorporates race (Black vs. non-Black) as a variable and the appropriateness of this has been questioned as race is a social and not a biological construct.[62] Nevertheless, using the current CKD-EPI formula without race as a variable results in lower eGFR values for Black individuals[63] and runs the risk of 2 potentials problems as follows: (i) Black patients would not be offered certain chemotherapies due to a having a lower eGFR and (ii) underdosing of drugs in Black patients. Measuring GFR would solve this issue, but is not practically feasible. Alternatively, new creatinine-cystatin C eGFR equations omitting race as recently reported by Inker *et al.*[64] are more accurate and resulted in smaller differences between Black and non-Black participants. Therefore, the National Kidney Foundation/American Society of Nephrology Task Force on reassessing the inclusion of race in diagnosing kidney disease recently recommended national efforts to facilitate increased, routine, and timely use of cystatin C.[65,66]

Over the past several years, it has been established that the performance of the CKD-EPI equation in the cancer patient population is superior over other methodologies.[56] We would recommend that the CKD-EPI equation is adopted as the de facto standard

regression equation to determine GFR in patients with cancer. In addition, several studies in cancer patients have recently shown that estimation of creatinine clearance using the Cockcroft and Gault formula is suboptimal and should be replaced by eGFR estimation by the CKD-EPI equation, because this is associated with more precise estimation of kidney function, more precise determination of cancer drug-eligibility, more accurate dose calculation, and prevention of chemotherapy-related adverse events.[67–73]

The discussion about whether body surface area (BSA)-indexing should be used or not is multifaceted and complex. The goal of BSA-indexing is to make GFR estimates comparable between subjects. In contrast, for drug dosage guidance, the aim should be to get the most precise estimate of the individual's capacity to excrete a particular drug or drug metabolite. BSA-indexing of GFR was proposed based on the assumption that BSA is reliable parallel to the amount of functioning kidney tissue. However, this assumption is highly questionable.[74–76] Furthermore, the reference value for BSA of 1.73 $m^2$ is based on an article of Moller *et al*. in 1928.[77] However, more recent BSA estimates demonstrate that nowadays the mean BSA for men and women are considerably higher (1.97 $m^2$ and 1.72 $m^2$, respectively,[78] or even 2.22 $m^2$ in the general Caucasian population[79]). As far as drug dosage adaptation is concerned, both the FDA and the European Medicines Agency recommend the use nonindexed GFR. We agree and would recommend absolute GFR to calculate individual drug chemotherapy dosage and express individual kidney function. The output of the CKD-EPI formula can be easily converted to absolute values through multiplication by patient's BSA per 1.73 $m^2$).[80]

A major caveat with the use of GFR estimating equations is that cancer patients who are ill may be in a nonsteady-state condition, a situation where estimating equations are likely to be inaccurate. These changes in GFR over time were demonstrated in a large retrospective evaluation of patients with solid tumors without CKD.[81] Patients had an average decline in GFR of 7 ml/min per 1.73 $m^2$ after 2 years of diagnosis or a CKD stage decline from stage 2 to 3 or 4.[81] In another study, the risk of AKI was 17.5% and 27% in the first and fifth year of cancer diagnosis, respectively, demonstrating that GFR is changing in a substantial number of cancer patients.[82] In these circumstances, the use of GFR estimating equations may give false values. This issue highlights the need for direct and real-time measurements of GFR at the point-of-care. This ability would allow for adjustment of drug dosing based on accurate assessment of measured GFR. There are now 2 methodologies in development that allow for direct quantitative GFR measurement that may simplify acquisition of this critical data. One technique uses a novel fluorescein carboxy-methylated dextran (rapidly filtered by the kidney) and the other uses a transdermal sensor to measure the removal of a fluorescent tracer from the blood.[83,84] Both of these methods would allow for a new paradigm of care where patients might be expected to get measured GFR levels just before drug dosing. The measured GFR would be used to adjust the dose of chemotherapy to ensure maximal efficacy and minimal toxicity. In addition, these techniques could be used during drug development to develop more precise dosing guidelines.

## Kidney Transplant Patients

In most clinical trials in oncology and hematology, organ transplant patients are excluded. This is due to the inherent nature of being on immunosuppressive agents and the resulting complexities of treatment protocols. Even within the kidney transplant patient trials, older patients excluded and number of trials are limited.[85] Post-transplant lymphoproliferative disorder is a well-studied cancer after organ transplant. In a large meta-analysis done on treatment strategies, the authors only found case series and retrospective designed studies for their evaluation.[86] Few randomized controlled trials specifically oriented for kidney transplant patients with skin cancer do exist.[87] Use of immunotherapy in the organ transplant patient is starting to increase. Recent analysis has shown increased rejection rates but also good efficacy.[88] Including organ transplant patients in trials of immunotherapy is going to be even more challenging for the oncology community in comparison to nontransplanted patients with CKD.

## Obtaining Pharmacokinetic and Pharmacodynamic Data Concerning Novel Anticancer Agents in CKD Patients With Cancer

Ideally, pharmacokinetic and pharmacodynamic data should be obtained during phase 1 and phase 2 trials of novel anticancer agents in patients with CKD. The pharmacokinetic data obtained from these trials are necessary to allow for dose adjustment for various degrees of kidney dysfunction. These are complex issues and require timed dosing and drug level measurement but are needed to better understand the influence of kidney dysfunction on drug disposition and effect.

## Novel Trial Designs and Interpretation

When designing new trials, sponsors may use templates from previous trials that excluded patients with

advanced kidney disease. These protocols may not have involved input from nephrologists who have the greatest knowledge and expertise regarding the unique characteristics of patients with kidney disease. Without specific efforts to target patients in this subgroup, investigators may be unable to recruit and enroll sufficient numbers of patients to draw meaningful conclusions about this population. Solutions to improve these barriers could include seeking guidance from patients themselves on what are best ways to optimize their willingness to join such trials. Similar strategies that have been applied in other CKD studies and leverage those practices as was done in the CREDENCE trial.[11,89] As per recent American Society of Clinical Oncology Friends of Cancer Research Joint Research Statement, widening the criteria for trial participation will take a concerted effort from investigators, trial sponsors, patients, and drug regulators (Figure 1).[90]

Future clinical trials need to recruit patients from all racial and ethnic backgrounds, and include patients from under-represented populations to help increase the diversity of clinical trial participants.[44] Therefore, approaches to clinical trial recruitment should be redefined and diverse patient communities should be consulted and engaged before, during, and after the design process. Patient participation in the design phase will result in increased trust from currently under-represented and difficult-to-reach populations.

Electronic health records (EHRs) have a huge potential to support data-driven optimization of participant selection toward improved statistical power of clinical trials. Kim *et al*.[91] used EHR data to perform a hypothetical trial to evaluate how adjusting threshold common eligibility criteria could enlarge the pool of people able to take part, and so improve the statistical power of clinical trials. Recently, Liu *et al*.[92] reported a software tool to optimize the inclusiveness and safety of eligibility criteria for cancer trials emulating clinical trials using EHR data. In their article, they report a tool called Trial Pathfinder, an open-source artificial-intelligence tool that uses EHR data to compare the outcomes of patients who did or did not receive a particular approved drug treatment. They estimated whether a treatment of interest affected the probability of individuals in the treatment group surviving the time frame studied (27 months after therapy began).[92] These researchers found that if the eligibility criteria were standardized to align with those of the trials that had had successful recruitment and had used more relaxed laboratory thresholds, this would enhance trial diversity. In the setting of cancer trials, trial eligibility could be increased by 53%, on average, and achieve a lower overall survival hazard ratio without increasing the toxicity risk to participants.[92]

## Development of Clinical Trial Consortiums

In oncology, clinical trial consortiums have been successful for decades in addressing the multiple research needs of patients with rare cancer subtypes, and have been instrumental in evaluating new cancer treatments and chemotherapeutic regimens. Similar clinical trial consortiums for patients with CKD and with cancer could help to stimulate the evaluation of novel anticancer drugs for this patient population and increase patient accessibility to clinical trials. Ideally, clinical trial consortiums could team-up with initiatives such as the Patient Network recently launched by the National Kidney Foundation, a US registry of persons with kidney disease, because both patients and researchers can use the Patient Network to find clinical trials of interest and to recruit participants, respectively.

## Practical Recommendations

It is unrealistic and unnecessary to perform dedicated outcome studies for every new anticancer agent in patients with CKD. In regards to the type of data required and the timing of the study in patients with CKD, we would recommend the following: every novel agent should undergo evaluation during phase I for renal elimination, thus providing pharmacokinetic data to allow dose adjustment for various degrees of kidney dysfunction. Practically, we would recommend evaluation for renal elimination in phase I in every novel agent in patients with CKD with a eGFR between 30 ml/min and 60 ml/min.

Concerning the optimal timing of studies in patients with CKD, a distinction should be made between drugs with and without significant renal elimination. With respect to nonrenally eliminated drugs, patients with up to CKD stage 3 or 4 should be included in phase 3 studies. To encourage sponsors to do so, a specific 'severe renal insufficiency' cohort could be used to include patients with eGFR between 15 ml/min and 30 ml/min. As previously suggested, there should be the option to exclude the outcome results from this cohort from the overall analysis and this cohort is mainly used to establish the safety of the cancer agent in this specific patient population. Including these patients in phase 3 studies would enhance patient enrollment and trial diversity, and make the study population more identical to the ultimate patient population. As regards dialysis-dependent patients, they could either be included in the phase 3 "severe renal insufficiency" cohort or, more realistically, there should be a postregistration commitment to perform additional postmarket studies in this patient population.

For drugs cleared by the kidneys, the risks associated with these drugs are higher so the situation

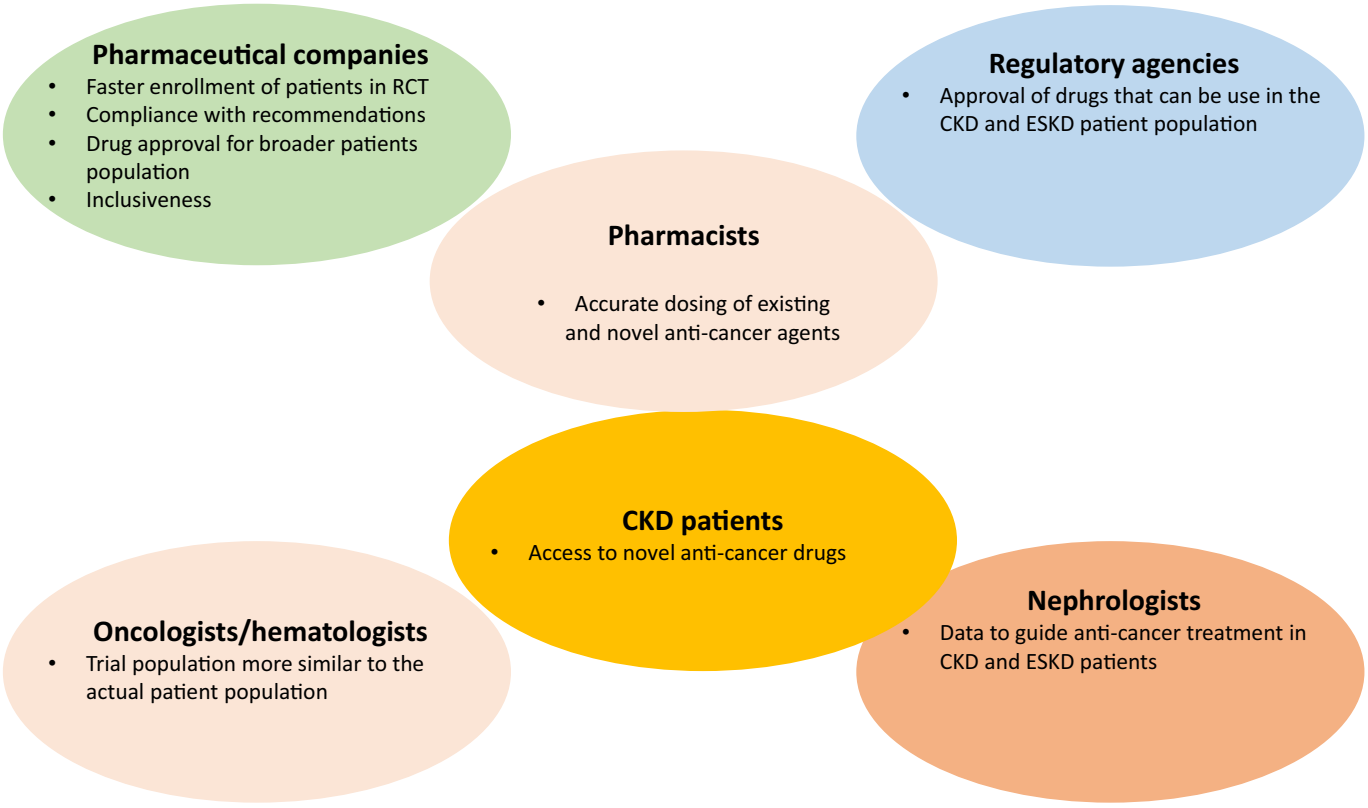


**Figure 1.** The various stakeholders involved in trial designs for patients with cancer with kidney diseases. CKD, chronic kidney disease; ESKD, end-stage kidney disease; RCT, randomized controlled trial

becomes more complicated and the inclusion of patients with kidney dysfunction in clinical trials will be highly dependent on the willingness to accept these risks by patients, physicians, and pharmaceutical companies. As novel cancer drugs could improve outcomes greatly, the willingness to include patients with CKD in clinical trials is expected to be great for both patients and physicians. In our opinion, including patients with CKD stages 4 to 5 in phase 3 trials will be difficult and might slow down the study progress and impedes its outcomes. Therefore, for these drugs, we would also recommend postmarket commitment studies after phase 3 studies in the general population. An important approach to improve patient recruitment for these types of studies could be a registry of preconsented CKD 4 to 5 patients with cancer and this should be explored for feasibility. These registries including CKD 4 to 5 patients with cancer could be connected study centers to build a hub-and-spoke model.

## Conclusion

Most trials use eligibility criteria that restrict participants to patients with low-risk profiles and exclude those who are pregnant, elderly, or have comorbidities besides the disease of interest. Eligibility criteria applied in cancer trials have become fairly generic and are frequently used as a uniform template across trials without clear scientific or clinical rationale. Using unnecessarily restrictive eligibility criteria slows patient recruitment, limits patients' eligibility for clinical trials, and most importantly leads to trial results obtained in populations that are not fully representative of the general patient population that will ultimately use or need the drug.[93,94] Furthermore, translating randomized controlled trial efficacy results to patients encountered in routine clinical care whose characteristics differ from those of the trial population results in notable gaps in the realized real-world efficacy.[95] Broadening cancer trial eligibility criteria to include patients with kidney dysfunction can maximize trial diversity, enhance the generalizability of trial results, and improve our capacity to understand the therapy's benefit-risk profile across the patient population in clinical practice in which the drug will be administered. This approach will ultimately avoid jeopardizing patient safety while extending therapies to patients who are currently excluded.

We believe that eligibility criteria for patients with CKD in clinical cancer trials should be simplified, be made less restrictive, and be better justified clinically (particularly related to imaging studies) than is currently the case. Furthermore, use of EHR data (in combination with trial enrollment data) and data-driven algorithms appear to be promising to improve

trial enrolment and maintain safeguards for participants.[92,96]

Sponsors should seek and incorporate feedback from nephrologists and patients with CKD throughout the development process, including patients from underrepresented populations. In addition, innovative trial designs with a separate parallel trial for patients with CKD (such as phase 3 CKD) or, after a phase 3 has been completed and the drug is ready for approval, a phase 1 is done for patients with CKD and ESKD to ensure mainly safety and dosing of the medication.[97] We agree with recently published position statement by the National Kidney Foundation entitled "Research Priorities for Kidney-Related Research—An Agenda to Advance Kidney Care" that the establishment and support of clinical trial consortiums would represent an important instrument to increase the number of clinical trials including cancer patients with CKD and recruitment of patients for these trials, in collaboration with platforms such as the recently launched Patient Network of the National Kidney Foundation.[98]

## DISCLOSURE

MHR serves on the data safety monitoring boards for clinical trials for Travere, Astra-Zeneca, and Reata and serves as consultant for Baxter. KDJ is a consultant for Astex Pharmaceuticals, Natera, GlaxoSmithKline, ChemoCentryx, Chinook and Travere Therapeutics, and is a paid contributor to UpToDate.com, and receives honorarium from ISN and ASN. BS is a senior clinical investigator of The Research Foundation Flanders (FWO) (1842919N) and received funding from the Foundation against Cancer (grant number grant C/2020/1380). SML is supported by the National Cancer Institute Cancer Center Support Grant (P30CA008748). MAP declared no competing interests.

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