REVIEW ARTICLE

The need for changes in clinical trials for improving cancer care for patients with CKD

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ABSTRACT

The majority of chemotherapy drugs used to treat cancer have limited therapeutic indices and potentially dangerous side effects. Since many cancer medications are at least partially excreted through the kidney, reliable information on the safe and efficient dosage of these medications in patients with Chronic Kidney Disease (CKD) is crucial for assisting in treatment decisions. Initial clinical studies for new drugs frequently only include patients with normal or barely compromised renal function. A small number of individuals with more severe kidney disease are included in further preregistration studies. Data from patients with End Stage Kidney Disease (ESKD) requiring kidney replacement therapy or severe renal impairment (here defined as an estimated Glomerular Filtration Rate (eGFR) 30 ml/min or stage 4G CKD) are particularly important. Data from this group are only seldom included in new drug applications submitted to the US Food and Drug Administration (FDA), which is particularly limited prior to drug registration. Unfortunately, a manufacturer's statement that a drug is contraindicated in patients with advanced kidney disease may be the consequence of a lack of data or other safety concerns, which prevents these patients from getting access to potentially helpful medications. This persistent issue of the systemic exclusion of cancer treatment trial participants with CKD hampers the provision of the best possible clinical care for these patients and highlights issues of inclusion, diversity, and equity. Additionally, as the population ages, more and more people with CKD and cancer are dealing with these problems. In this study, we assess the scientific justification for excluding CKD patients from cancer trials and provide an all-encompassing solution.

Keywords: Cancer chemotherapy; Chronic kidney disease; Clinical trials; Onconephrology

INTRODUCTION

According to studies, 50% of cancer patients have impaired kidney function and must change their dose of at least one anticancer medication due to the kidneys varying levels of clearance. To guarantee that therapeutic levels are reached for medications that are eliminated by the kidney and to prevent side events, a thorough understanding of kidney function is required. Unfortunately, because patients with severe kidney illness are typically not included in clinical trials, many anticancer medications lack information on the proper dosage when kidney function is reduced [1].

264 (85%) of clinical therapy trials for the five most prevalent cancers published in high impact factor journals excluded the great majority of patients with kidney impairment, according to a study on 310 anticancer drug trials involving 282,889 patients. Surprisingly, in 62% of patients, the exclusion criteria were serum creatinine threshold values rather than Glomerular Filtration Rates (GFRs). Given that renal dysfunction is frequent among cancer patients, excluding these patients makes it more difficult to gather data on possible drug side effects in this population and restricts access to cancer medicines that might help patients with kidney dysfunction [2].

Patients with CKD are frequently excluded from clinical trials that assess treatments without renal clearance or a high risk of nephrotoxicity (e.g., immunotherapies and hormonal therapies). These treatments frequently offer significant potential substitutes for well-established, nephrotoxic chemotherapy regimens that are really cleared. Access to potentially helpful anticancer treatments is further hampered by the lack of information on the use of these medications in CKD patients [3].

Importantly, it is generally known that CKD is marked by significant racial, socioeconomic, and ethnic differences. The most recent high impact randomized clinical trials in nephrology also revealed a dearth of non-white populations, despite the fact that non-white racial groups are more susceptible to kidney disease and its associated comorbidities. Since CKD patients are routinely excluded from clinical trials, resolving this issue will increase clinical trials' diversity and inclusivity [4].

Sponsors may be wary of funding oncological trials involving patients with CKD, especially those with advanced disease, as this could potentially skew their efficacy and safety results and have an impact on regulatory approval and product labeling. Patients with CKD present a unique challenge for oncology trials. It's important to note that patients with CKD experience a similar predicament in cardiovascular disease studies. The systematic exclusion of patients with kidney failure from late-phase clinical trials should be avoided, even if it may be warranted in some situations, such as phase I trials where the metabolism and excretion of medicines may not be known [5].

Patients with CKD generally face three obstacles while applying to participate in cancer trials. The following are a few of these difficulties: (i) Worries of the trial sponsor (ii) The planning and execution of studies, and (iii) The absence of a reliable trial infrastructure in nephrology [6].

Clinical studies are expensive, time consuming, and frequently stressful for patients. The inability to show safety and efficacy, exorbitant expenses to produce the treatment, difficulty finding and enrolling patients who match eligibility requirements, and underpowered trials that fail to achieve statistical significance for their end points are some of the typical reasons why trials fail. In most clinical trials, it is normal practice to exclude patients with renal function in the range of a GFR of 60 ml/min due to the fact that CKD might add substantial concern for proper dosage and perhaps enhance the risks of adverse effects of chemotherapeutic drugs. Notably, a study found that the most frequent exclusion standards for participants enrolling in cancer clinical trials were creatinine threshold values rather than eGFR.

The inclusion of patients with advanced CKD in cancer trials is seen as being significantly hampered by safety issues. Patients with CKD frequently experience adverse events and experience drug-drug interactions since they have several comorbid conditions and are taking numerous drugs. Patients may not be allowed to participate in a trial if there is a chance that the

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intervention will aggravate their CKD or have unfavorable effects. Some ways to fix this include creating new study designs, banning or restricting medications that interact with study drugs, learning how investigational products affect eGFR and/or serum creatinine levels, and managing the risks of exacerbating CKD progression complications and/or electrolyte disorders. Although cooperation amongst nephrology specialists is necessary, these difficulties may be treatable [7].

Patients with CKD and ESKD may not use several end points used in the general population, and conflicting comorbidities may make it more difficult to analyze study results. Hemodialysis patients had a higher mortality risk from causes other than cancer compared to nondialyzed patients, according to a retrospective analysis of 675 individuals. The long term hemodialysis patients participating in the multicenter CANDY (CANcer and DialYsis) research were treated with anticancer medication. This study found that inappropriate high dosing of chemotherapy drugs was more frequently associated with hematological, gastric, and neurologic side effects than was appropriate low dosing, and that 44% of patients developed iatrogenic toxicity in relation to inappropriate dose adjustment due to the lack of management recommendations in this specific group of patients.

Renal failure can result in drug buildup, which raises toxicity, as kidney excretion is crucial for the removal of anticancer drugs. This problem might be solved by enabling sponsors to enroll patients with CKD and/or ESKD, but to omit them from their critical efficacy analysis when submitting it to the FDA. Another feasible alternative is to do a parallel study for important cancer medicines in people with CKD and/or ESKD (phase 3 CKD). As an alternative, cancer specific end points should be taken into account in patients with CKD and/or ESKD (cancer specific mortality instead of overall mortality). Finally, early involvement of nephrologists and CKD patients in the creation of such trial protocols may be beneficial.

Because individuals with CKD are thought to be unable to safely conduct diagnostic examinations with either iodinated contrast or gadolinium based contrast, the presence of renal disease may also be incompatible with imaging studies used in clinical cancer trials. Excluding patients with CKD from these studies due to worries 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. This is because these clinical trials frequently require contrast based radiologic evaluation to assess tumor burden and response.

The underlying concern is whether individuals with CKD are really at high risk for the supposed toxicity from these medications, even if this seems to be a logical exclusion criterion for clinical trials that evaluate drug efficacy and toxicity. Importantly, not all degrees of CKD have the same risk of toxicity. However, it is believed that all patients with stage 3 CKD (eGFR 60 ml/min per 1.73 m^2) and higher have a similar risk. Additionally, i.v. contrast used in computed tomography scans carries a reduced risk of nephrotoxicity than arterial contrast injections. The same holds true for GBCM, where the gadolinium chelate type and contrast dose have a significant role in determining the risk for NSF in patients with CKD. The frequency of NSF is very high [8].

In the end, not including CKD patients in diagnostic contrast-based investigations that are required perpetuates an unnecessary clinical paradigm that is not backed up by data from actual clinical practice. The nephrology community, by restricting contrast exposure in patients with CKD, has really played a big role in advancing this relatively cautious strategy by initially focusing on IV contrast computed tomography scans. Iodinated contrast-associated AKI is relatively infrequent in people with CKD stages 1 to 3, even if it can happen in people with an eGFR below 30 ml/min per 1.73 m^2.

LITERATURE REVIEW

Kidney transplant patients

Organ transplant patients are typically not included in cancer and hematology clinical studies. Due to the fundamental nature of immunosuppressive medications and the ensuing complexity of treatment protocols, this is the case. Older patients are not included in kidney transplant patient trials, and there are not many trials.

An organ transplant related cancer with a good understanding is post-transplant lymphoproliferative disease. Only case series and retrospectively planned studies were found in a sizable meta-analysis on treatment options for the authors' assessment. There aren't many randomized controlled trials that are explicitly targeted at kidney transplant recipients with skin cancer. Immunotherapy is beginning to be used more frequently in organ transplant patients. Increased rejection rates, together with strong efficacy, have been revealed by recent studies. Comparing patients with CKD who have undergone organ transplantation to non-transplanted individuals will make it more difficult for the oncology community to include these patients in immunotherapy trials [9].

DISCUSSION

Obtaining pharmacokinetic and pharmacodynamical information on novel anticancer agents in CKD patients with cancer

Ideally, phase 1 and phase 2 trials of new anticancer medicines in patients with CKD should gather pharmacokinetic and pharmacodynamical data. These trials pharmacokinetic data are required to enable dose modification for varied degrees of renal impairment. To further understand the impact of renal disease on drug disposition and effect, these complicated concerns call for timed dosing and drug level assessment.

Innovative trial designs and interpretation

Sponsors may use templates from trials that excluded participants with advanced renal disease in the design of new trials. The nephrologists who have the most knowledge and experience about the particular traits of individuals with renal illness may not have provided input for these regimens. Without making a special effort to find patients in this subgroup, researchers might not be able to find and enroll enough patients to make valid inferences about this population.

In order to overcome these obstacles, it may be helpful to consult the patients themselves for advice on how to maximize their willingness to participate in such trials. The credence trial used similar methods that have been used in other CKD investigations and that make use of such techniques. According to a recent joint research statement from the American society of clinical oncology and friends of cancer research, expanding the trial participation requirements will need coordinated efforts from researchers, trial sponsors, patients, and drug regulators.

To help expand the variety of clinical trial participants, future clinical studies must enroll patients from all racial and ethnic origins as well as individuals from underrepresented populations. Therefore, methods for recruiting patients for clinical trials need to be rethought, and varied patient communities need to be informed and included before, during, and after the design phase. Increasing patient involvement in the design process will boost trust from underrepresented and hard to reach demographics.

In order to increase the statistical power of clinical trials, Electronic Health Records (EHRs) have a great deal of promise to help data driven optimization of participant selection.

In a study, researchers performed a hypothetical trial using EHR data to assess how altering common eligibility criteria could increase the number of participants and, as a result, increase the statistical power of clinical trials.

Construction of clinical trial consortiums

Clinical trial consortiums in oncology have long been effective in meeting the various research demands of patients with uncommon cancer subtypes and have been crucial in the evaluation of novel cancer therapies and chemotherapeutic regimens. Similar clinical trial consortiums for cancer and CKD patients can encourage the assessment of innovative anticancer

medications for this patient population and improve patient access to clinical trials. The national kidney foundation recently launched the patient network, a US registry of people with kidney disease. The patient network can be used by both patients and researchers to find clinical trials of interest and to recruit participants, so it would be ideal if clinical trial consortiums collaborated with initiatives like this one [10].

CONCLUSION

Most trials contain eligibility requirements that limit participants to individuals with minimal risk profiles and disqualify those who are pregnant, old, or have comorbid conditions in addition to the study's primary condition. Cancer trial eligibility requirements are now rather broad and frequently employed as a standard template across trials without a clear scientific or clinical justification. Unnecessarily stringent eligibility requirements slow down patient recruitment, restrict patients eligibility for clinical trials, and, most critically, provide trial results that are not entirely representative of the patient group that will ultimately use or require the treatment. Additionally, there are noticeable gaps in the real world effectiveness when randomized controlled trial efficacy results are applied to patients receiving routine clinical care and whose features differ from those of the trial population. It is possible to maximize trial diversity, improve the generalizability of trial findings, and strengthen our ability to comprehend the benefit risk profile of the therapy across the patient population in the clinical practice where the drug will be administered by extending cancer trial eligibility criteria to include individuals with kidney dysfunction. By using this strategy, medications will eventually be made available to patients who are currently excluded without endangering patient safety.

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