Seminars in Dialysis

DRUG THERAPY: SPECIAL CONSIDERATIONS IN DIALYSIS PATIENTS

Anticancer Drugs in End-Stage Kidney Disease Patients

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ABSTRACT

The increased incidence of malignancies in patients with chronic kidney patients and especially in end-stage kidney disease (ESKD) patients has been discussed since the mid-1970s. Consequently, oncologists, nephrologists, and pharmacists are increasingly facing challenging situations of cytotoxic drug handling in dialysis patients because of pharmacokinetic modifications. In these patients, two main issues must be considered. First, the absence of renal function in hemodialysis (HD) patients may necessitate drug dosage reduction. Therefore, drug prescription must be cautiously checked before administration with appropriate dosage adjustment whenever necessary to ensure efficacy while avoiding overdosage and related side effects. Second, drug clearance by dialysis session must be taken into account for appropriate chemotherapy timing administration to avoid drug removal, which may result in a loss of efficacy. These two main considerations must not be considered as a contra-indication to chemotherapy in ESKD patients, but more as a need for an individualized prescription according to available recommendations.

Since the demonstration in the 1940s that hemodialysis (HD) can sustain life and relieve the symptoms of uremia, the widespread access to dialysis that began in the 1970s has been life-saving for patients with acute renal failure or end-stage kidney disease (ESKD). Today, over 1 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. Substantial improvements of chronic renal replacement therapy have led to prolonged survival. Despite conflicting results among various studies in the 1990s, there is now sufficient epidemiologic evidence to conclude that there is a higher incidence of at least some cancers in dialysis patients (1–6).

Chronic kidney disease (CKD) and cancer are connected in a number of ways in both directions (7). Cancer can cause CKD either directly or indirectly through the adverse effects of therapies (chemotherapy, radiation). Conversely, CKD may be a risk factor of cancer: chronic oxidative stress, compromised immune system, viral infections (such as viral hepatitis B and C, Epstein–Barr virus), some drugs used for glomerulonephritis or vasculitis (such as azathioprine and cyclophosphamide) and some renal disease, such as acquired cystic kidney disease (7).

Whatever the mechanisms are, the fact is that an increasing number of patients are presenting ESKD and cancer and that more and more physicians are more likely to face the question of anticancer drug handling in ESKD patients, because of the potential pharmacokinetic modifications of these drugs in this population. These modifications may concern the four pharmacokinetic phases (absorption, distribution, metabolism, excretion).

Absorption

While chemotherapies are frequently administered intravenously some anticancer drugs are used orally. Impaired drug metabolism has been shown in patients with CKD and may be the cause of a significant increase in oral bioavailabity (8). There are many physiological changes, for example: changes in gastric pH may affect the absorption of some oral drug by changing their state of ionization. Moreover, changes in the integrity of the intestinal wall in CKD patients have been reported, due to asymptomatic intestinal inflammation observed in these patients (9,10). This inflammatory condition results in increased gut permeability and in increased drug absorption. 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 in the effects of hepatic first-pass metabolism (11,12). All these changes may

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potentially lead to an increased drug exposure in CKD patients.

On the opposite, some pharmacokinetic data has reported the opposite phenomenon for the targeted therapy sunitinib, which seems to be less well absorbed orally in ESKD patients as compared to those with normal renal function (13).

Distribution

The plasma protein binding of many drugs is decreased in CKD patients. Hypoalbuminemia, frequent in CKD patients, together with the accumulation of endogenous substances, which competitively displace acidic drugs from their binding sites on albumin, and a conformational change in the binding sites on the albumin molecule are the main explained mechanisms (8,14,15). Acidic drugs usually bind to albumin, but basic drugs have a high affinity for α1-acid glycoprotein but often also bind to albumin and lipoproteins. Although the plasma binding of basic drugs appears to be generally unaffected in CKD patients, it may be increased for some drugs because α1-acid glycoprotein is an acute phase protein, that is, elevated in hemodialysis patients (8,15,16). Therefore, the unbound fraction of the drug is increasing, leading to potential dose-related side effects.

The volume of distribution of drugs is potentially significantly increased in CKD patients (8,16). This abnormality may be the result of fluid overload, decreased protein binding, or altered tissue binding. For example, an abstract, presented at the European Society of Medical Oncology 2014 Congress, reported that the unbound concentrations of SN-38 (an active metabolite of irinotecan) were higher in severe CKD patients than those with normal kidney function. The author reported that the inhibition of SN-38 protein binding by an uremic toxin, the 3-carboxy-4methyl-5-propyl-2-furanpropionate was the possible mechanism (Fujita K. Change in plasma protein binding of SN-38, an active metabolite of irinotecan, in cancer patients with severe renal failure (poster 483p). European Society of Medical Oncology 2014 Congress, Madrid, Spain.)

Metabolism

Pharmacokinetic studies in CKD patients have shown that nonrenal clearance is reduced for many drugs, especially in HD patients (8,15). First publications were concerning antibacterial drugs and warfarin (17,18). But it concerns also anticancer drugs, like vandetanib for which an increase in the systemic exposure and drug clearance were reported in CKD patients (19,20). The fact that CKD can potentially affect the activity of various drug-metabolizing processes is not easy to accept, but it is a reality and impacts not only the metabolizing enzymes of the cytochrome but also other drug-metabolizing enzymes, such as N-acetyltransferase (8). The main explanation is that uremic toxins that accumulate in the body in CKD patients modify the activities of these enzymes and also of the hepatocyte transporters (21,22).

Prodrug, Active Metabolites

Some anticancer drugs are prodrugs. It is a pharmaceutical substance which is administered in an inactive form and, once absorbed, is metabolized into an active form (e.g., capecitabine). Furthermore, in other cases, both the parent compound and its metabolite(s) are active. The pharmacological activities may depend of all active substances. Therefore, if the active compound(s) is (are) not generated properly, the treatment will not be efficient and the body will accumulate a useless drug. On the other side, if the metabolized inactive compound(s) is (are) not generated properly, the body will accumulate the active parent compound.

Furthermore, it is also important to consider the pharmacokinetics of the metabolites, because they are usually eliminated by further metabolism and/or renal excretion. These metabolites (active or not active) may also be responsible for dose-related side effects. Consequently, the altered pharmacokinetics of all active/inactive compounds of the parent drug has to be considered when adjusting the dosage in CKD patients (8). For example, all oral targeted tyrosine kinase inhibitors are metabolized by cytochrome P450 enzymes to produce active metabolites (23). Of course, the accumulation of nontoxic, inactive metabolites is not a problem.

Finally, independently of renal function, drugs with the same metabolism pathway and with the same receptor on the metabolic enzyme can compete with each other; leading to a drug–drug interaction and affecting their metabolism. For the same reason, coadministration with an enzymatic inhibitor or inductor can lead to an overdosage or under dosage, respectively, of the drugs using the same pathway.

Renal Excretion

There are three different mechanisms of renal excretion: glomerular filtration, tubular secretion and tubular reabsorption. Unbound protein drugs and small size drugs (<30 kDa, enough to pass through the glomerular membrane) are eliminated by the glomerular filtration. Secretion and tubular reabsorption are implicating active transport mechanisms and involve different transporters.

There are three different types of renal tubular transporters: Organic Anion Transporters (OAT), Organic Cation Transporters (OCT) and P-glycoprotein transporters (P-gp) (24).

In CKD patients, these three mechanisms of excretion may be more or less altered, depending on the nature of renal disease. Thus, changes in the expression and activity of these transporters have been reported in CKD patients, inducing changes in the renal excretion of drugs.

According to the intact nephron hypothesis, the function of all segments of a diseased nephron is assumed to be equally affected (25). Consequently, it is assumed that, regardless of the intrarenal pathways of excretion, the loss of excretory function in the diseased kidney can be quantified by glomerular filtration rate (GFR) (8). However, the GFR is negligible in HD patients.

Independently of renal function, drug substances secreted by the same transporters can compete with each other; in doing so, they may affect their renal clearances and can cause a drug–drug interaction.

Immune Dysfunction

CKD patients, especially ESKD patients, are immunocompromised (26). 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). Its main consequence is a higher risk of infection and an impaired immune response to vaccination. Therefore, usual vaccination schedules are less efficient and it is necessary to potentially modify the dosage of vaccines in HD patients.

This pharmacodynamic modification in ESKD patients is not concerning fortraditional chemotherapy, but the coming therapeutic cancer vaccines and the immunotherapeutic anticancer drugs may encounter difficulties in ESKD patients. For example, the anticytotoxic T-lymphocyte antigen-4 (CTLA4) antibody ipilimumab was approved for the treatment of advanced melanoma. CTLA4 counteracts the costimulatory signal from CD28, by competitively binding to its ligands on the surface of antigen-presenting cells (27). Tumor cells use this pathway to turn off the immune response by suppressing the activation and proliferation of conventional T cells and promoting the function of regulatory T cells which can dampen the immune response at the tumor site (28,29). By blocking CTLA4, ipilimumab restores the costimulatory activity of CD28, thereby increasing the number of activated T cells that can migrate and attack the tumor.

Therefore, a question arises: what would happen in immunocompromised ESKD patients? Would the immune dysfunction of ESKD patients compromise the mechanisms of anti-CTLA4? In theory, there is a risk of inefficiency in case of CKD because of the impaired immune response. Furthermore, the same theoretical risk rises for other immunotherapic anticancer drugs, such as anti-PD1 (nivolumab, pembrolizumab) or anti-PDL1/PDL2.

Dialysis

ESKD patients are potentially at risk of drug accumulation and thus at dose-related adverse events in case of overdosage, as seen previously. Most ESKD patients are treated with chronic hemodialysis and continuous ambulatory peritoneal dialysis. These procedures are designed to remove toxic waste products that accumulate in ESKD patients. However, they can also remove drugs prematurely and be responsible of a potential under dosage and therapeutic inefficiency.

Therefore, ESKD patients are facing two treats. First, an over dosage because of a drug accumulation, an appropriate dosage adjustment is therefore necessary for avoiding dose-related adverse events. Second, drug clearance by dialysis must be taken into account for appropriate chemotherapy timing of administration to avoid drug removal, which may result in a loss of efficacy. It is important to consider both problems before prescribing anticancer drugs in ESKD patients. The dialyzable drugs must be administered after dialysis session in HD patients. However, nondialyzable drugs can be given after or before the dialysis session in HD patients. Very little is known about anticancer drug management in HD patients and even less about the optimal timing and necessary dosage adjustments depending on dialysis sessions. Finally, there are only few data and studies in peritoneal dialysis patients.

Anticancer Drugs Use in ESKD Patients

The dosage of anticancer drugs used in ESKD patients frequently requires dosage reduction to avoid severe toxic effects. Therefore, careful dosage adjustment is mandatory to optimize exposure to anticancer drugs and to reduce the risk of adverse effects. The CANDY (CANcer and DialYsis) study reported that 72% of the dialysis patients received at least one drug that required a dosage adjustment or for which there were no data about drug dosage adaptation in dialysis patients (30). In these patients, 82% had drugs requiring administration after dialysis sessions. Overall, 88% of the patients who received anticancer drugs needed a specific drug management regarding dose adjustment and/or time of administration according to the dialysis session of at least one anticancer drug. These results underline that ESKD patients are routinely receiving anticancer drugs that require dosage adjustment and a specific time of administration (for HD patients). The main difficulty is to find adequate recommendations in this population.

Such recommendations can be found on a website (SiteGPR, www.sitegpr.com) available in both English and French languages for more than 800 International Nonproprietary Names (INN) of drugs, including 75 INN of anticancer drugs. Of these 75 drugs, SiteGPR actually provides a recommendation

for 68.0% of anticancer drugs in ESKD patients. For the remaining 32.0%, it is possible to ask the website team for a specific recommendation. Consequently, SiteGPR is able to propose a dosage for 100% of the anticancer drugs (after asking for specific recommendations). The study of these 75 anticancer drugs' summary of product characteristics (SmPCs) reported that there was no usable recommendation for 76.0% of these anticancer drugs in ESKD patients. This observation underlines that SmPC is not an adequate and useful source of information for prescribing anticancer drugs in ESKD patients.

Conclusion

Chemotherapy used in ESKD patients is a growing concern as the risk of cancer is increased in ESKD patients (7). However, because of pharmacokinetic modifications in these patients, it is necessary to adapt the dosage of chemotherapy and other anticancer drugs. It is also important to consider that ESKD is not an automatic absolute contra-indication to these treatments. However, most drugs require a specific renal management in ESKD patients, in terms of drug dosage and time of administration regarding the dialysis session (30). Indeed, the clinical risks for the ESKD cancer patients are (i) developing extra-renal toxicity because of the increase in drug systemic expositions and (ii) having inefficient drug exposure because of early extensive elimination throughout dialysis. To prevent these two problems, it is crucial to use the available recommendations (31) and tools (32) to treat such patients adequately. Furthermore, pharmacokinetics studies are warranted in dialysis patients.

This specific management is not just important for ESKD patients but also for all CKD patients, because of the high prevalence of CKD in cancer patients. Indeed, when the renal function was estimated with the aMDRD formula in solid tumors patients, 52.9% and 50.2% of the patients in the two studies IRMA-1 and IRMA-2, respectively, had a reduced GFR (<90 mL/min/1.73 m^2) and 12.0% and 11.8% were diagnosed with CKD (<60 mL/min/1.73 m^2). Therefore, it is also important to correctly adapt the dosage of anticancer drug in these patients.

Earlier this year, the Cancer & the Kidney International Network (www.c-kin.org) was founded which aims at raising awareness on these issues, and developing education (annual conference), guidelines, and clinical research projects in this specific field.

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