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Running head: Pharmacology of TKI in kidney diseases

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Abstract:

Tyrosine kinase inhibitors (TKI) have introduced a significant advancement in cancer management. These compounds are administered orally, and their absorption holds a pivotal role in determining their variable efficacy. They exhibit extensive distribution within the body, binding strongly to both plasma and tissue proteins. Often reliant on efflux and influx transporters, TKI undergo primary metabolism by intestinal and hepatic cytochrome P450 enzymes, with non-kidney clearance being predominant. Due to their limited therapeutic window, many TKI display considerable intra- and interindividual variability. This review offers a comprehensive analysis of the clinical pharmacokinetics of TKI, detailing their interactions with drug transporters and metabolic enzymes, while discussing potential clinical implications. The prevalence of kidney conditions, such as acute kidney injury (AKI) and chronic kidney disease (CKD), among cancer patients is explored in terms of their impact on TKI pharmacokinetics. Lastly, the potential nephrotoxicity associated with TKI is also examined.

Keywords

Tyrosine Kinase inhibitors, pharmacokinetics, drug-drug interactions, cytochromes, transporters, kidney diseases, metabolism

Abbreviations

ABC	ATP-binding cassette
AKI	Acute kidney injury
ALK	Anaplastic lymphoma kinase
ATN	Acute tubular necrosis
AUC	Area under the curve of concentrations in time; exposure
BCR-ABL	Breakpoint Cluster Region - Abelson murine Leukemia
BCRP	Breast cancer resistance protein
CKD	Chronic kidney disease
Cmax	Maximal concentration
c-MET	Mesenchimal epithelial transtition factor
CYP	Cytochrome P450
EGF	Epidermal growth factor
eGFR	Estimated glomerular filtration rate
EGFR	Epithelial growth factor receptor
EMA	European medicines agency
FDA	US Food and drug administration
FGFR	Fibroblast growth factor receptor
FMO	Flavin-containing monooxygenase
GFR	Glomerular filtration rate
GLUT	Glucose transporter
HER	human epidermal growth factor receptor
KDIGO	Kidney Disease Improving Global Outcomes
KRT	Kidney replacement therapy
MATE	Multi-antimicrobial extrusion protein
OAT	Organic anion transporter
OATP	Organic anion transporting peptide
OCT	Organic cation transporter
PDGFR	Platelet-derived growth factor receptor
P-gp	P-glycoprotein
SCr	Serum creatinine
SLC	Solute carriers
TKI	Tyrosine kinase inhibitor
TMA	Thrombotic microangiopathy
TRPM6	transient receptor potential cation channel, subfamily M, member 6
UGT	UDP-glycosyltransferase
VEGFR	Vascular endothelial growth factor receptor

Introduction

Our understanding of the mechanisms governing tumorigenesis and cancer progression has led to the development of targeted therapies. Among these, tyrosine kinase inhibitors (TKI) play a key role in disrupting signal transduction pathways triggered by various oncogenes.[1] Their targeted actions enhance efficacy while limiting toxicity. TKI include both large molecules -like antibodies- and small molecules, multikinase inhibitors, which will be discussed in this review.

TKI are classified into several families, including anti-epithelial growth factor receptor/ human epidermal growth factor receptor 1 (EGFR/HER1) (afatinib, erlotinib, gefitinib, lapatinib, osimertinib), anti-HER2 (lapatinib), anti-anaplastic lymphoma kinase/ROS Proto-Oncogene 1 (ALK) (alectinib, ceritinib, crizotinib), anti-vascular endothelial growth factor receptor (VEGFR) (axitinib, cabozantinib, lenvatinib, pazopanib, regorafenib, sorafenib, sunitinib and vandetanib), and anti-BCR-ABL (breakpoint Cluster Region - Abelson murine Leukemia) (bosutinib, dasatinib, imatinib, nilotinib).

TKI are administered orally, improving patient convenience and treatment flexibility. However, this represents an extra challenge in terms of therapeutic adherence, as patients exhibit considerable intra-individual and inter-individual variability due to many pharmacokinetic parameters and a narrow therapeutic window.[2–4] Unraveling these factors can help control them, improve drug effectiveness and minimize toxicity. Indeed, exposure to TKI is strongly affected by drug-drug interactions, genetic polymorphisms, associated pathologies and cancer types.[5,6] Hence, renal carcinoma is highly associated with pharmacokinetic alterations, since kidneys play a major role in TKI elimination.[4]

Here we present (1) a descriptive analysis of the relevant clinical TKI pharmacokinetics, (2) a summary of kidney adverse effects observed in oncology, and (3) an overview of the impact of kidney pathologies on TKI pharmacokinetics and related dose adjustments.

Clinical TKI pharmacokinetics

(1) Absorption

Absorption contributes significantly to the inter-individual variability of TKI response. This is due to their high liposolubility resulting in slow dissolution in the gastrointestinal tract. This variability is probably amplified by individual differences in the extent of enterohepatic circulation.[7] The solubility of most TKI depends on local pH. Since TKI are weakly basic, there is an equilibrium between the ionized and non-ionized forms that depends on intragastric pH. At normal acidic intragastric pH (pH range 1-2), the equilibrium shifts to the ionized form. Since the latter has better solubility, absorption from the gastrointestinal tract is optimal at low intragastric pH; however, when pH is increased, the balance shifts towards the non-ionized form. Consequently, bioavailability, maximal concentration (Cmax), and area under the curve (AUC), are decreased, potentially resulting in treatment failure.

Intragastric pH is increased both in the postprandial period and after acid-suppressive drug intake. The impact of the latter is minor to moderate. Thus, eight TKI (bosutinib, ceritinib, dasatinib, erlotinib, gefitinib, lapatinib, nilotinib, pazopanib) present a mild clinical relevance, scored as AUC changes, when administered concomitantly with acid-suppressing drugs.[8] In these cases, the general recommendations

of US Food and Drug Administration (FDA) and European Medicines Agency (EMA) are: (1) minimizing the use of acid-suppressive drugs, and (2) separating their administration from TKI intake by 2 to 4 hours before or 3 to 4 hours after.

TKI absorption is also influenced by meal fat content. Co-administering with a high-fat meal may induce significant increases or decreases in Cmax and/or AUC (Table 1). Recommendations include taking medication either without food to avoid the effect of quantitative and qualitative variations in meal intake, or with a low-fat meal.

(2) Distribution

Some parameters characterize drug distribution, including exposure (Cmax), volume of distribution and protein binding. TKIs are lipophilic, extensively distributed in tissues -including tumors-, and present a large volume of distribution after administration.[3,9] Another important parameter is their binding to plasma and tissue proteins, which may limit their diffusion into tissues. Most TKIs are at least 90% bound to plasma proteins such as albumin, α-1-acid glycoprotein and/or lipoproteins.[3,4,6,9] In some pathological conditions such as cancer, malnutrition, kidney or hepatic failure, or nephrotic syndrome, albumin concentration may decrease. Conversely, inflammatory conditions are associated with increased levels of α-1-acid glycoprotein from 2- to 5-fold. Both albumin and α-1-acid glycoprotein have high-affinity and low-capacity properties for drug binding. When two drugs that bind the same protein are administered, they compete for binding sites, which can increase the release of free forms and potentially lead to toxicity.

Finally, tissue distribution of TKIs also depends on their influx or efflux mediated by transporter proteins located in cell membranes, as discussed below.

(3) Metabolism

After reaching the portal vein, TKIs are metabolized in the liver (Figure 1). Phase I enzymes, including the cytochrome P450 family (CYP), promote TKI metabolism (Table 2). Conversely, few drugs are conjugated by phase II enzymes, such as UDP-glycosyltransferases. The activity of most cytochrome enzymes can be modified by certain conditions like age -often enhancing-, and inflammation -reducing-.[10] Therefore, drug concentrations tend to decrease with age and increase with inflammation.

Common foods such as garlic and grapefruit inhibit, whereas St John's wort strongly induces CYP3A4, modulating drug availability and exposure [11] Likewise, smoke, caffeine, and alcohol induce some cytochromes, such as CYP1A2. Hence, drug-drug interactions with potent CYP inhibitors and inducers must be considered when establishing TKI dosage (Table 3)[5].

Consequently, TKI exposure may decrease over time. This phenomenon is observed when sorafenib is administered to hepatocellular carcinoma patients through three potential mechanisms: first, autoinduction of CYP3A4/5 metabolism; [12,13] second, intestine overexpression of the ATP-binding cassette (ABC) subfamily G member 2 (ABCG2) efflux protein, limiting absorption;[13] and third, activation of other metabolic pathways, like those modifying liver expression of UDP-glycosyltransferase 1A9.[12,14]

Furthermore, other drug interactions may affect TKI metabolites. For example, sorafenib-glucuronide excreted into the gut lumen can be cleaved by microbial enzymes into sorafenib, which is then reabsorbed, supporting its persistence in systemic circulation.[15]

(4) Elimination

Some parameters characterize drug elimination, notably clearance. In the case of TKIs, which undergo hepatic metabolism, non-kidney clearance is preponderant, while kidney clearance is relatively low, affecting only TKI metabolites.

Apparent elimination half-lives are often large except for some TKI, such as dasatinib and axitinib, which present a very short apparent period (2 and 3 hours respectively).[3,8]

(5) Drug transporters

Drug transporters are widely expressed, especially in gut, bile ducts, kidneys and blood-brain barrier (Figure 1).[9] Membrane transporters can have clinically relevant effects on drug pharmacokinetics and pharmacodynamics by controlling absorption, distribution, and elimination.

Efflux drug transporters like P-glycoprotein (P-gp), ABC subfamily B member 1 (ABCB1), and breast cancer resistance protein (BCRP; ABCG2), release TKIs into the intestinal lumen.[16] Thus, inhibition of these efflux transporters at the intestinal level leads to increased absorption and therefore increased drug concentrations.

Other efflux drug transporters contributing to TKI bioavailability are those included in the multidrug resistance protein subfamily (ABC subfamily C member 1 to 12, like MRP1) and the multi-antimicrobial extrusion protein (MATE; solute carrier family 47) (Figure 1). As efflux transporters, inhibition of their activity results in decreased drug levels.

Several uptake transporters may be involved as well, such as organic ion transporting peptide (OATP, SLCO), organic anion transporters (OAT; SLC22), and organic cation transporters (OCT; SLC22). These influx proteins promote the entry of TKI into the cll. Therefore, inhibition of their activity results in increased drug levels.

Several TKI also inhibit MATE-1 and OCT2, notably at the basolateral and apical membranes of kidney tubular epithelial cells.[17,18] These carriers participate in the secretion of certain endogenous analytes, such as creatinine.

Most TKIs (notably afatinib, lapatinib and pazopanib) are substrates of P-gp and BCRP transporters, which can interact with other drugs that are either substrates, inducers or inhibitors of these carriers (Table 2). Consequently, it is recommended to avoid strong P-gp inducers and BCRP inhibitors and to monitor side effects when using P-gp and BCRP substrates.

Likewise, some TKIs may inhibit several drug transporters. The clinical relevance of drug-drug interaction regarding drug transporters is negligible for some TKIs and the combination with inhibitory or inducing compounds is well tolerated. Elsewhere, transporters may be implicated in the resistance to conventional and target-specific anti-tumor drugs. This condition often involves ABC transporters, which could attenuate the potency of chemotherapeutics.[15,19,20] Therefore, inhibition of efflux transporters may

reverse cancer cell resistance. This could result in increased diffusion of transporter substrates towards their site of action.[21–26] Nephrotic syndrome can affect the activity of these transporters in kidney, liver, and duodenum, leading to decreased absorption, metabolism, and excretion.[27]
Finally, substrates of these transporters can interfere with endogenous substances produced in some pathological conditions, such as systemic inflammation and chronic kidney failure.[28] This interaction induces a decrease in drug efflux or influx, with a long-term risk of inefficiency or toxicity.

(6) Pharmacogenomics

Many polymorphisms in genes encoding metabolism enzymes and drug transporters that may have a clinically relevant impact[29] .Nevertheless, the FDA only defines a relationship between the risk of drug accumulation and genetic polymorphisms of CYP2D6 for gefitinib given its poor metabolism.[30] Conversely, other polymorphisms in CYP encoding genes have minor impact on TKI metabolism.[31]

From a pharmacodynamic perspective, the FDA also defines some polymorphisms affecting TKI safety. This is the case for HLA-DRB1*07:01 and HLA-DQA1*02:01, responsible for lapatinib hepatotoxicity.[30] Likewise, UGT1A1*28/*28 is linked to the hyperbilirubinemia induced by nilotinib and pazopanib, while HLA-B*57:01 accounts for liver enzyme rise associated with pazopanib.

Kidney pathologies in oncology

Both acute kidney injury (AKI) and chronic kidney diseases (CKD) are highly prevalent in patients with solid tumors.[32] Among critically ill cancer patients, AKI is developed in 13 to 54%,[33] CKD in 13 to 30 [34,35] and dialysis is required in 8 to 60% of patients.[36] Similarly, organ transplant recipients have an increased risk of cancer because of immunosuppression. Some cancers with large masses may present tumor lysis syndrome,[37] causing hyperuricemia, hyperkalemia, hyperphosphatemia, metabolic acidosis and AKI.
Kidney disease increases the risk of nephrotoxicity induced by cancer treatments and may compromise their administration. Major AKI risk factors include nephrotoxic anticancer drugs, cancer-related metabolic troubles, tissue deposition of paraproteins and nephrotoxic non-chemotherapeutic drug treatments.[32] Nephrotoxicity is increased with patient's age, intravascular volume depletion and previous AKI or CKD occurrence.

Impact of kidney pathologies on TKI pharmacokinetics

In addition to highly fluctuating drug exposure linked to interindividual variability in each pharmacokinetic process -as described in the first sections-, kidney pathologies can have an impact on the pharmacokinetics of certain drugs, which prompts the development of personalized therapeutic drug monitoring.[39] A relationship between exposure and response and/or safety has been established and therapeutic targets have already been reported for some drugs.[40,41]

Systemic physiologic changes are very dynamic in AKI patients. Drug clearance and distribution vary in the short term (some hours and days) and it is difficult to practically quantify the glomerular filtration rate (GFR)[42] as well as liver metabolism. While absorption may be reduced, the volume of distribution is usually unchanged but sometimes increased. In the AKI context, hepatic clearance can be affected especially when hepatorenal syndrome and cytokine release syndrome are associated. Hepatorenal syndrome, resulting from decompensated cirrhosis, presents splanchnic vasodilatation and arterial hypovolemia, resulting in decreased TKI distribution volume. The inflammation observed in hepatorenal and cytokine release syndromes leads to increased proinflammatory cytokines. These cytokines moderately inhibit CYP3A4, 1A2, 2C9, 2C19, decreasing TKI clearance between 2-fold and 2.6-fold, thereby increasing their exposure.[43,44] In AKI, kidney drug excretion is diminished, yet this reduction can manifest rapid changes.[42,45] Furthermore, the high interindividual variability in pharmacokinetics represents a considerable challenge, and therapeutic drug monitoring is strongly recommended.[40,42,45]

Kidney adverse effects in the TKI era

(1) AKI

In 2021, the Kidney Disease Improving Global Outcomes (KDIGO) clinical guidelines defined AKI as: (1) an increase in serum creatinine (SCr) concentration by more than ≧0.3 mg/dL (26,5 mmol/L) within 48 hours; (2) an increase in SCr by ≥50% within 7 days; or (3) oliguria (urine volume <0.5 mL/kg/h) by ≥4 hours. Based on creatinine levels, AKI is classified as stage 1 (1.5x< SCr <2x baseline), 2 (2x< SCr <3x baseline), or 3 (SCr >3x baseline).

Two features need to be considered when a TKI is used, regardless of its original target: (1) although TKI targets a selective signaling pathway involved in the oncogenic process or in metastasis, whether or not its relevant TK receptor displays genetic alteration, it actually acts on multiple signaling pathways and therefore displays multikinase activity. (2) Most renal transporters are concentrated on proximal renal tubules, at the apical (MATE1 and MATE2-K) and basolateral (OAT2, OCT2, OCT3) sides (Figure 1). (3) Some TKI are predominantly marketed as anti-angiogenic (on-target effect) but they may inhibit kidney transporters (off-target effect). This is the case of cabozantinib, regorafenib and axitinib. However, many TKIs (notably cabozantinib, crizotinib, imatinib, ceritinib and alectinib) interfere with active tubular creatinine secretion by kidney transporters, mimicking AKI.[17,18,46,47]. Among the large TKI spectrum, the strong inhibitors of tubular creatinine secretion include members of the ALK-ROS1 family (crizotinib). Inhibition of tubular transport is lesser with cabozantinib relatively to crizotinib. Cystatin-C is a small molecule (15 kDa) freely filtered by glomeruli and not secreted by tubules. Therefore, Cystatin-C clearance is a good alternative to serum creatinine to estimate GFR (eGFR) in patients under TKI therapy. Thus, a significant increase in SCr without a parallel modification of Cystatin-C suggests false AKI by kidney transporter inhibition. Conversely, a severe increase in SCr correlated with a Cystatin-C rise is likely not to be due to kidney transporter inhibition and requires eventually a kidney biopsy for diagnosis. It must be taken into consideration that, in the presence of an inflammatory syndrome, Cystatin-C may significantly increase and result in GFR underestimation. A serious concern is related to the use of the antidiabetic drug metformin, which is excreted in urine by active tubular secretion

mediated by OCT2 and MATE 1/2-K. In patients under TKI and receiving this medication, a severe adverse effect (lactic acidosis) may occur. This should be prevented by either significant reduction of doses or cessation.

TKI may induce AKI through glomerular damage and/or toxic injury to kidney tubules (Figure 2 and Table 5). Glomerular injuries, including TMA and podocytopathy, are mostly reported in patients under TKI targeting predominantly the VEGFR signaling pathway (cabozantinib, lenvatinib, axitinib, sunitinib, sorafenib and pazopanib)[48–53]. According to the FDA, axitinib, dasatinib, gefitinib, sorafenib, sunitinib and vandetanib have the highest odds ratio for all nephropathies within TKI. Axitinib and sorafenib increase 3-fold to 4-fold the risk of developing glomerulopathy and/or nephrotic syndrome, while pazopanib and sunitinib present a relative risk increase of 2-fold for both side effects.[32] Several types of AKI occur with members of the TKI family acting against the BCR-Abl fusion protein (imatinib, dasatinib), consisting of TMA, podocytopathy, acute tubular necrosis (ATN) and electrolyte disorders, most of them reversible with TKI cessation.

ATN, biopsy-proven, was reported in patients treated with ALK-TKI crizotinib and alectinib.[54,55] Studies on kidney toxicity induced by TKI, histologically documented, are scarce. Electrolyte disorders, mainly related to tubular transport inhibition, are frequent and have been reported with several TKI families, such as EGFR, ALK and BCR-ABL inhibitors. They include hyponatremia, hypomagnesemia and hypokalemia. Hyperkaliemia was reported under axitinib in a patient developing distal tubular dysfunction (type 4 renal tubular acidosis),[56] while other TKI (imatinib, sunitinib and ceritinib) may induce hypophosphatemia, resulting from inhibition of the FGF23/FGFR pathway-mediated proximal tubule secretion, while other TKI (imatinib, sunitinib and ceritinib) may induce hypophosphatemia.

(2) CKD

A few studies have focused on patients with CKD, nephrectomy or in hemodialysis (Table 4).[57] CKD is characterized by a progressive decline in eGFR, such that kidney function is relatively stable over weeks or months. While CKD is frequently observed in cancer patients, many oncologic strategies interfere with kidney function.[45,58,59] CKD induces some changes in drug pharmacokinetics[60,61], as drug absorption may increase or decrease, though it is poorly quantified. Animal and human studies indicate that drug absorption may increase because of impairment of the gut wall barrier function. Additionally, enzymatic metabolism and efflux transporter activities are decreased in enterocytes, inducing increased bioavailability of lipophilic drugs and thus an increase in serum drug levels. Hence, the volume of distribution is either unchanged or increased because of a better diffusion and/or a decrease in efflux protein activities. Protein binding may be altered because of lower protein concentration. This effect may be increased in cancer patients because of malnutrition or sarcopenia. A decrease in drug clearance by several CYPs has been observed, resulting in kidney failure, while extra-kidney elimination is unaltered or possibly decreased.[38,45] Drug clearance may be altered because of low protein influx activities.[62] Accumulation of uremic toxins is observed concomitantly with the progression of kidney failure.[61] These toxins act through activation of the aryl hydrocarbon receptor, leading to transcriptional activation of some CYP, UGT and transporter genes in hepatocytes and kidney tubular cells.[38,45,59]Indoxyl sulfate,

kynurenine, kynurenic acid, and indole-3-acetic acid are the major uremic toxins and ligands for the aryl hydrocarbon receptor. In addition, these toxins can directly inhibit both enzymes and transporters and participate in the altered drug clearance in CKD patients.

Limited data are available about TKI pharmacokinetics in patients with kidney failure (Table 4). For mild kidney impairment (60 mL/min < eGFR < 89mL/min), no changes are described except for cabozantinib and unbound vandetanib, without clinical relevance. For moderate kidney failure (45 mL/min < eGFR < 59 mL/min), exposure is increased for afatinib, bosutinib, imatinib and unbound vandetanib, but dose reduction is recommended only for imatinib. For severe kidney impairment (30 mL/min < eGFR <44 mL/min), exposure to crizotinib is also increased without recommendation, while imatinib, lenvatinib and vandetanib exposures are increased, necessitating dose adjustments.

Likewise, a higher total exposure to imatinib was observed in patients with mild, moderate and severe kidney impairment.[63] As imatinib excretion in urine is less than 13%, it might be explained by decreased activity of hepatic metabolic enzymes, resulting in decreased imatinib clearance. Another possible explanation might be the upregulation of acute phase proteins, such as α-1-acid glycoprotein, which has been described both in patients with cancer and with kidney impairment.

Both CKD and cancer lead to hypoalbuminemia. If the latter coexists with impaired drug clearance, unbound drug levels increase and induce drug toxicity. In addition, kidney impairment might alter patients' sensitivity to anticancer drugs even if drug exposure is unaffected. An example is the increased toxicity of sorafenib in patients with varying degrees of kidney impairment, even if sorafenib exposure is not altered.[64] In conclusion, kidney impairment not only affects kidney excretion of active compounds and metabolites, but can also influence the exposure–toxicity relationship for anticancer drugs.

(3) **Nephrectomy and** renal carcinoma

TKI treatment handling is complex and requires close monitoring, especially in patients having undergone unilateral nephrectomy for metastatic renal carcinoma. In a nephrectomized rat model, expression and activity of some metabolizing enzymes and efflux transporters have been found changed in intestine and liver.[60,61] The clinical impact of these modifications has been studied.[57]

Following unilateral nephrectomy, the remaining kidney experiences a rapid compensatory hypertrophy, associated with increased kidney blood flow.[67] Various mechanisms act together to promote compensatory hypertrophy, including activation of the PI3 kinase-mTORC-S6 kinase pathway,[68,69] proliferation of mesangial cells secreting growth factors (hepatocyte growth factor, epidermal growth factor, insulin-like growth factor 1), whereas genes involved in growth inhibition are suppressed.[70] Another major metabolic change occurs in the remaining kidney to maintain water and sodium balance. Experimental studies suggest that glomerular hemodynamic alterations occur, resulting in hypoxia, notably in the tubulointerstitial compartment. Indeed, activation of the hypoxia inducible factor is another major determinant of compensatory hypertrophy, through the active transcription of vascular endothelial growth factor, platelet-derived growth factor, erythropoietin and GLUT -1. Collectively, these data may explain why TKI use in patients with unilateral nephrectomy leads to glomerular alterations and acute kidney failure, as TKI inhibit the mechanism involved in compensatory hypertrophy.

(4) Kidney replacement therapy (KRT)

KRT increases elimination of hydrophilic drugs. Drug clearance in patients undergoing hemodialysis is determined by drug properties, dialysis conditions, and patient characteristics. Most TKI are highly protein-bound and predominantly cleared by liver, and therefore unlikely to be removed by conventional hemodialysis. For drugs metabolized above 50% by kidneys, elimination is increased by KRT. Intermittent KRT is efficient but usually of short duration, and has a minimal effect when the drug is administered after KRT. Conversely, continuous KRT often requires an increase in maintenance dosing. Peritoneal dialysis has minimal additional effects on chronic drug therapy.

Kidney impairment might alter other pharmacokinetic processes and requires dose adjustment.[58] No pharmacokinetic changes are indicated except for sunitinib and dasatinib (Table 4).[65,66] Indeed, no clinically relevant differences in sunitinib and its active metabolite exposure have been observed in CKD patients. Yet, in patients requiring hemodialysis, a 47% reduction of sunitinib and metabolite exposure was observed.[65] Since sunitinib is not removed by hemodialysis, the decreased exposure was probably a result of lower drug absorption. In our experience, no change in the minimal concentration of cabozantinib was observed before and after hemodialysis (personal data).

Conclusion

Owing to the high complexity of TKI pharmacokinetics, their therapeutic drug monitoring is highly recommended, as well as the control of their interactions with other drugs.

Given the current gaps in data and mechanistic understanding, there is a pressing need for comprehensive studies involving patients with CKD, under periodic dialysis, and transplanted , treated with TKI.

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Figures

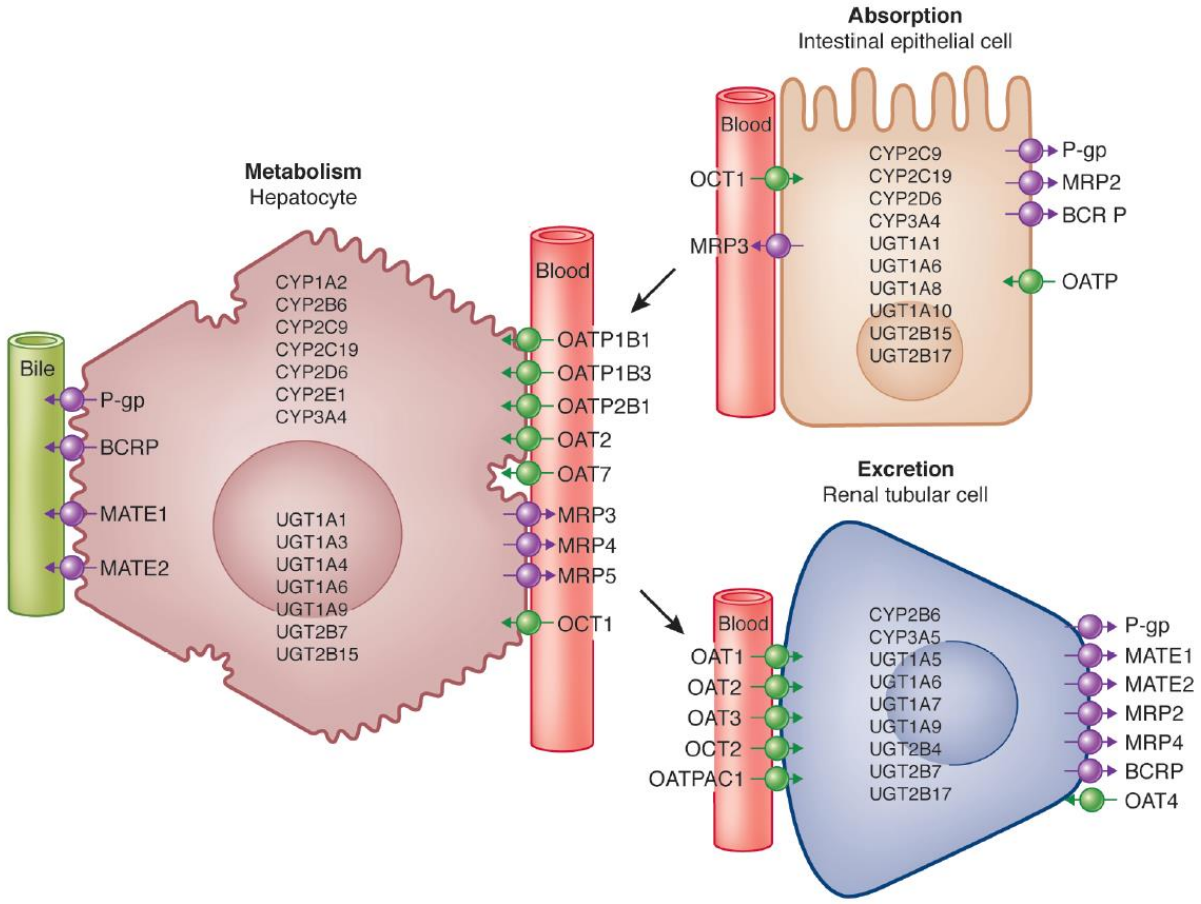

Figure 1: Overview of drug transporters and metabolizing enzymes for the main organs involved in the pharmacokinetics of TKI.

BCRP: Breast cancer resistance protein; CYP: cytochrome P450; MATE: multi-antimicrobial extrusion protein; MRP: multidrug resistance protein; OAT: organic anion transporter; OATP: organic anion transporting peptide; OCT: organic cation transporter; P-gp: P-glycoprotein; UGT: UDP-glycosyltransferase.

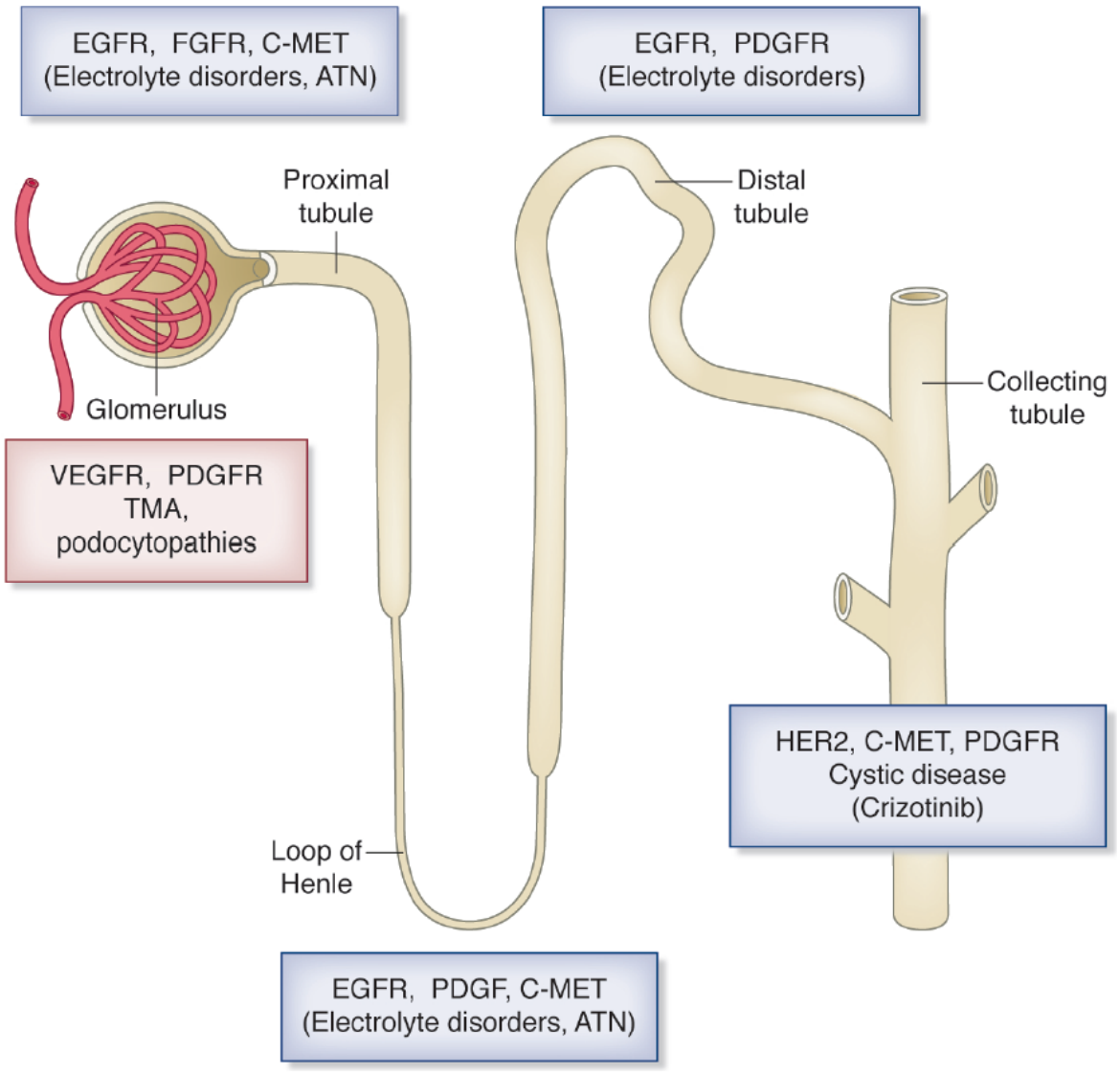

Figure 2. Glomerular damages and/or renal tubule injuries induced by TKI depending on their selective mechanism of action (ATN: acute tubular necrosis, EGFR: epithelial growth factor receptor, FGFR: fibroblast growth factor receptor; PDGFR: platelet-derived growth factor receptor, VEGFR: vascular endothelial growth factor receptor, c-MET: mesenchymal epithelial transition factor).

Tables

Table 1: Clinically significant modifications of maximal concentration (Cmax) and/or area under the curve of concentrations in time (AUC) of TKI with due to US Food and Drug Administration (FDA) and European Medicines Agency (EMA) recommendations.

	Change in Cmax	Change in AUC	FDA/EMA recommendations	Reference
Afatinib	-50 %	-39 %	Take without food	[71]
Alectinib	+170 %	+192 %	Take with food	[72]
Axitinib	High-fat, high-calorie meal +11 % Moderate-fat, standard-calorie meal -16 %	High-fat, high-calorie meal +19 % Moderate-fat, standard-calorie meal -10 %	Take with or without food	[73]
Bosutinib	+128 %	+152 %	Take with food	[74]
Cabozantinib	+41 %	+57 %	Take without food	[75]
Ceritinib	+41 to +58 %	+39 to +73 %	Take with food	[76]
Crizotinib	-14 %	-14 %	Take with or without food	[77]
Dasatinib	N/A	+14 %	Take with or without food	[11]
Erlotinib	+64 %	+109 %	Take without food	[78]
Gefitinib	+32 %	+37 %	Take with or without food	[79]
Imatinib	-11 %	-7 %	Take without food	[80]
Lapatinib	+90 to 166 %	+80 to 160 %	Take without food	[81]
Lenvatinib	-2 to +6 %	-5 to 0 %	Take with or without food	[82]
Nilotinib	+33 to +112 %	+15 to +82 %	Take without food	[83]
Osimertinib	-8 %	+6 %	Take with or without food	[84]
Pazopanib	+108 to +110 %	+92 to +134 %	Take without food	[85]
Regorafenib	+54 to +73 %	+36 to +48 %	Take with food or low-fat meal	[11]
Sorafenib	N/A	-30 %	Take without food	[11]
Sunitinib	+4 % (-23 % for SU12662)	+12 % (-8 % for SU12662)	Take with or without food	[86]
Vandetanib	-11 %	0 %	Take with or without food	[87]

N/A: Not available.

Table 2: Major and minor metabolism enzymes of TKI, interaction with drug transporters and indication of their inhibitory or inducing activity on CYPs and transporters.

	Major CYP	Minor CYPs and others	Drug transporters	CYPs and transporters inhibitory activity	CYPs inducing activity
Afatinib	N/A	N/A	P-gp, BCRP	*In vitro* P-gp, BCRP	N/A
Alectinib	CYP3A4	N/A		*In vitro* P-gp, BCRP	N/A
Axitinib	CYP3A4	CYP3A5, 1A2, 2C19, UGT1A1	P-gp, BCRP	UGT1A4,7,9, CYP1A2, *in vitro* P-gp	N/A
Bosutinib	CYP3A4	FMO	P-gp, BCRP	N/A	N/A
Cabozantinib	CYP3A4	CYP2C9	MRP2	CYP2C9, 3A4, 2C19, *in vitro* P-gp, BCRP, MATE1, MATE2	N/A
Ceritinib	CYP3A4	N/A	P-gp	CYP3A4, 2C9, 2A6, 2E1	CYP3A4
Crizotinib	CYP3A4	CYP3A5, 2C8, 2C19, 2D6	P-gp	CYP3A4, 2B6, UGT1A1, 2B7, P-gp, OCT1, OCT2	UGT1A1, CYP2B6, 2C8, 2C9
Dasatinib	CYP3A4	FMO, UGT	P-gp	CYP2C8, 3A4, MATE1, MATE2, OCT2, OATP1B1, OATP1B3	N/A
Erlotinib	CYP3A4	CYP1A2, 1B1, 3A5	P-gp, BCRP	CYP1A1, 3A4, 2C8, UGT1A1, *in vitro* OCT2, OAT3	N/A
Gefitinib	CYP3A4	CYP3A5, 2C19, 2D6	P-gp, BCRP, MRP7	CYP2D6, 2C19, *in vitro* P-gp, BCRP	UGT1A1, UGT1A7, UGT1A9, UGT2B7
Imatinib	CYP3A4	CYP3A5, 1A2, 2D6, 2C9, 2C19	P-gp, BCRP, OCT1, OATP1A2, OATP1B3	CYP2C9, 3A4	N/A
Lapatinib	CYP3A4	CYP3A5, 1A2, 2D6, 2C8, 2C9, 2C19	P-gp, BCRP	CYP3A4, 2C8, *in vitro* P-gp, BCRP, OATP1B1	N/A
Lenvatinib	CYP3A4	N/A	P-gp, BCRP	CYP2C8, 1A2, 2B6, 2C9, 2C19, 2D6, 3A4, UGT1A1	CYP3A4
Nilotinib	CYP3A4	CYP2C8, 1A1, 1A2, 1B1	P-gp, BCRP	CYP2D6, 2C9, 3A4, 2C8, UGT1A1, P-gp, BCRP	CYP2D6, 2C8, 2C9
Osimertinib	CYP3A4	CYP3A5, 1A2, 2A6, 2C9, 2E1	P-gp, BCRP	CYP1A2, 2C8, 3A4, UGT1A1, P-gp, BCRP	CYP3A4, 1A2
Pazopanib	CYP3A4	CYP1A2, 2C8	P-gp, BCRP	CYP3A4, 2D6, 2C8, UGT1A1, *in vitro* P-gp, BCRP, OATP1B1	
Regorafenib	CYP3A4	UGT1A9	P-gp, BCRP	UGT1A1, 1A9, CYP2C8, 2B6, 2C9, 2C19, 3A4, *in vitro* BCRP	N/A
Sorafenib	CYP3A4	UGT1A9	P-gp, OATP1B1, OATP1B3, MRP2-3	CYP2B6, 2C8, 2C9, UGT1A1, P-gp	
Sunitinib	CYP3A4	CYP1A1, 1A2	P-gp, BCRP	P-gp, BCRP	N/A
Vandetanib	CYP3A4	FMO		In vitro P-gp, BCRP, OCT2	N/A

BCRP: Breast cancer resistance protein; CYP: cytochrome; FMO: Flavin-containing monooxygenase; MATE1: multi-antimicrobial extrusion protein 1; MATE2: multi-antimicrobial extrusion protein 2; MRP2: multidrug resistance associated protein 2; OAT3: organic anion transporter 3; OATP1B1: organic anion transporting peptide B1; OATP1B3: organic anion transporting peptide B3; OCT1: organic cation transporter 1; OCT2: organic cation transporter 2; P-gp: P glycoprotein; UGT: UDP-glycosyltransferase; N/A: Not available.

Table 3: Inducers and inhibitors of major cytochromes and phase II enzymes.

	Inhibitors	Inducers
CYP1A2	amiodarone, ciprofloxacin, fluvoxamine, norfloxacine, phenylpropanolamine	rifampicin, smoke
CYP3A4	amiodarone, amprenavir/fosamprenavir, aprepitant, atazanavir, boceprevir, ciprofloxacin, clarythromycin, diltiazem, erythromycin, fluconazole, indinavir, itraconazole, ketoconazole, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycine, verapamil, voriconazole	bosentan, carbamazepine, efavirenz, modafenil, oxybutynin, phenobarbital, phenytoin, primidone, rifabutin, rifampicin
CYP2B6	clopidogrel, sertraline, voriconazole	carbamazepine, cyclophosphamide, dexamethasone, efavirenz, modafinil, nevirapine, phenobarbital, phenytoin, rifampicin, ritonavir
CYP2C8	clopidogrel (metabolite), dasatinib, gemfibrozil, imatinib, nilotinib, sorafenib, trimehtoprim	dexamethasone, rifampicin
CYP2C9	amiodarone, atazanavir, clopidogrel, etravirine, fluconazole, fluoxetine, fluvastatin, fluvoxamine, gemfibrozil, imatinib, irbesartan, losartan, metronidazole, miconazole, quetiapine, sorafenib, valproic acid, voriconazole	bosentan, carbamazepine, dexamethasone, efavirenz, phenobarbital, phenytoin, primidone, rifampicin, ritonavir
CYP2C19	clobazam, esomeprazole/omeprazole, felbamate, fluconazole, fluoxetine, fluvoxamine, gefitinib, isoniazide, lansoprazole, moclobemide, modafinil, quetiapine, ticlopidine, voriconazole	dexamethasone, phenobarbital, phenytoin, primidone, rifampicin, ritonavir
CYP2D6	amiodarone, bupropion, chlorpromazine, citalopram, clomipramine, duloxetine, flecainide, fluoxetine, imatinib, levomepromazine, melperone, metoclopramide, moclobemide, nilotinib, paroxetine, promethazine, quetiapine, quinidine, risperidone, ritonavir, sertraline, sorafenib, terbinafine, venlafaxine	
CYP2E1	clomethiazole, disulfiram	ethanol, isoniazide, tobacco, cannabis
UGT		carbamazepine, lamotrigine, phenobarbital, phenytoin

Table 4: Impact of chronic kidney disease (CKD) and kidney replacement therapy (KRT) on pharmacokinetics of TKI.

	Kidney failure			KRT	References
	Mild (60 mL/min <eGFR<89 mL/min)	**Moderate** (45 mL/min <eGFR<59 mL/min)	**Severe** (30 mL/min <eGFR<44 mL/min)		
Afatinib		Increased AUC 22-39 %	Increased AUC 34-42 %	No change	88–90
Alectinib		No change		No change	91–93
Axitinib		No change		No change	51,94,95
Bosutinib	No change	Increased AUC 35 %	Increased AUC 60 %	No data	96
Cabozantinib	Increase AUC 30 %	No change	No data	No data	75
Ceritinib	No change		No data	No data	97
Crizotinib	No change		Increased AUC 79 %	No data	98,99
Dasatinib		No data		Increased concentration	66,100
Erlotinib		No change		No change	101
Gefitinib		No change		Not dialyzable	88,102
Imatinib	No change	Increased AUC 50 %	Increased AUC 100 %	No data	103,104
Lapatinib		No change		No change	105
Lenvatinib	No change	No change	Dose reduction change	No data	106
Nilotinib		No data		No data	107
Osimertinib		No change		No change	108,109
Pazopanib		No change		No data	50
Regorafenib		No change		No data	110
Sorafenib		No change		No change	48,111
Sunitinib		No change		Not dialyzable but decreased AUC	49,65
Vandetanib	Increased unbound AUC 46 %	Increased unbound AUC 62 %	Increased unbound AUC 79 %	No data	112,113

AUC: Area under the curve of concentrations in time; CYP: cytochrome, FMO: flavin-containing monooxygenase, UGT: UDP-glycosyltransferase

Table 5: Kidney adverse effects of TKIs.

Therapeutic class	Drug	Main kidney toxicities	Mechanisms
VEGFR inhibitors	axitinib, cabozantinib, lenvatinib, pazopanib, regorafenib, sorafenib, sunitinib, vandetanib	Arterial Hypertension (11-43%) AKI (7-33%) Proteinuria (7-49%) Nephrotic syndrome (1-15%) TMA Electrolyte disorders	Inhibition of the VEGF/VEGFR axis-mediated angiogenesis
EGFR/HER1 inhibitors	afatinib, erlotinib, gefitinib, lapatinib, osimertinib	Electrolyte disorders (Hypomagnesia Hypokaliemia Hyponatremia Hypophosphatemia)	Inhibition of epithelial Mg2+ channel TRPM6 (most frequent with EGFR-targeting antibodies)
ALK inhibitors	alectinib, ceritinib, crizotinib	AKI (acute tubular necrosis) Podocytopathy Electrolyte disorders Cystic disease (Crizotinib)	Inhibition of MET/HGF axis inhibition de IGF-1R
BCR-ABL inhibitors	bosutinib, dasatinib, imatinib, nilotinib	AKI TMA Electrolyte disorders Proteinuria	Inhibition of c-Kit, PDGFR Inhibition of Src kinases

VEGFR: anti-vascular endothelial growth factor receptor, EGFR: anti-epithelial growth factor receptor, ALK: anti-anaplastic lymphoma kinase, BCR-ABL: Breakpoint Cluster Region - Abelson murine Leukemia. TMA: thrombotic microangiopathy TRPM6: transient receptor potential cation channel, subfamily M, member 6.

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