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Major pitfalls of protein kinase inhibitors prescription: A review of their clinical pharmacology for daily use

Paul Gougis[a,b,*], Lola-Jade Palmieri[c], Christian Funck-Brentano[a,d], Angelo Paci[e], Ronan Flippot[f], Olivier Mir[f,g,1], Romain Coriat[c,1]

[a] Sorbonne Université, Faculty of Medicine, AP-HP, Pitié-Salpêtrière Hospital, Department of Pharmacology and Clinical Investigation Center, F-75013, Paris, France
[b] CLIP² Galilée, Pitié-Salpêtrière Hospital, F-75013, Paris, France
[c] AP-HP, Cochin Hospital, Department of gastroenterology and gastrointestinal oncology, Université Paris Descartes, Paris, France
[d] INSERM, CIC-1421 and UMR ICAN 1166, Institute of Cardiometabolism and Nutrition (ICAN), F-75013, Paris, France
[e] Service de Pharmacologie, Département de Biologie et Pathologie Médicales, Gustave Roussy et Université Paris Saclay, Villejuif, France
[f] Department of Medical Oncology, Gustave Roussy, 114 rue Edouard Vaillant, 94800, Villejuif, France
[g] Department of Ambulatory Care, Gustave Roussy Cancer Campus, Villejuif, France

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ABSTRACT

Protein kinase inhibitors (PKI) are a growing class of anticancer agents. They are prescribed with flat doses, and their oral administration is associated with interindividual variability in exposure. Patients can be over- or underexposed, due to numerous factors. We reviewed key pharmacokinetic concepts and mechanisms by which PKIs prescription could be altered. Challenging situations that could lead to increased toxicity or to therapeutic failure are described and recommendation for clinicians are proposed. Finally, the interest of therapeutic drug monitoring and indications for its use in daily practice is discussed.

1. Introduction

Protein kinase inhibitors (PKIs), including tyrosine kinase inhibitors, are small molecules (as compared to monoclonal antibodies) that inhibit the phosphorylation of tyrosine kinases or serine/threonine kinases. The physiological role of kinases is to transduce the signal of the binding of a ligand to an external tyrosine kinase receptor into a nuclear signal of proliferation or survival. For example, epidermal growth factor (EGF) physiologically binds to EGF receptor (EGFR), which in turn activates a series of phosphorylations that lead to the activation of transcription programs that promote cell proliferation.

Each PKI has a very variable spectrum of actions on the kinome which is composed of over 500 human proteins that have a phosphorylation activity (Manning et al., 2002).

PKIs can be divided into 2 categories: narrow spectrum or large spectrum:

- PKIs with a narrow spectrum are targeting oncogenic addiction (Weinstein and Joe, 2008). Erlotinib for EGFR-mutated lung adenocarcinoma or imatinib for c-KIT mutated gastro-intestinal stromal tumour are examples of such PKIs. They usually have a good tolerance profile.
- PKIs with very large spectrum of inhibition, like sunitinib or sorafenib, have a less favourable tolerance profile.

Many of these PKIs have been approved as anticancer drugs in the last fifteen years. Understanding the pharmacological properties of these drugs is critical for patient care since small variations in their blood concentrations might compromise the efficacy of the treatment or expose a patient to threatening adverse events. In this review, we present a summary of pharmacokinetics of PKIs, and discuss some pitfalls of their prescription. Finally we discuss the interest of Therapeutic Drug Monitoring (TDM) in clinical practice.

2. Basic pharmacokinetics concepts

2.1. AUC, dose and therapeutic index

PKIs' activity and toxicity are proportional to the Area Under the Curve (AUC, Fig. 1). Many of these molecules have a narrow therapeutic index, and are often toxic at therapeutic dose. AUC should be in the right range: if the AUC is too low, the drug might not be effective,

* Corresponding author at: Centre d'Investigation Clinique Paris-Est, Hôpital Pitié-Salpêtrière, 47-83 Boulevard de l'Hôpital, 75013, Paris, France.
E-mail address: Paul.gougis@aphp.fr (P. Gougis).
[1] Equal contribution.

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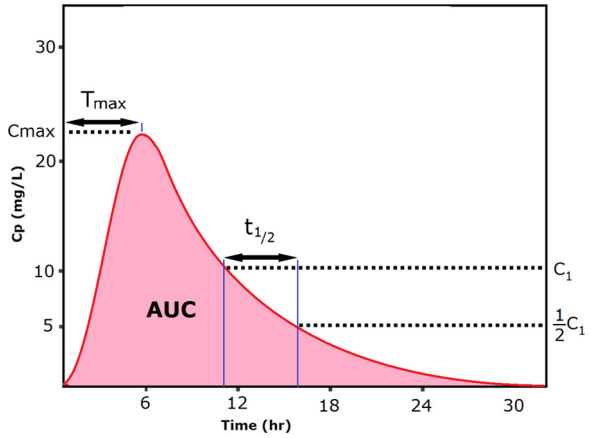

Fig. 1. Plasma concentration vs. time profile of a single oral drug administration.
Area under curve of a single dose of a drug administered orally. In the elimination phase (when the drug is fully absorbed), the concentration C_1 is divided by 2 after 1 half-life $t_{1/2}$
AUC: area under curve; C_p: plasma concentration of the drug; C_{max}: maximum plasma concentration; T_{max}: time to reach maximum concentration; $t_{1/2}$: terminal half-life

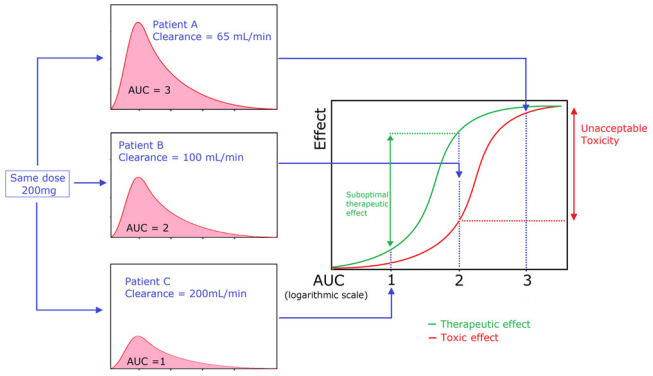

Fig. 2. Inter-individual variation of Area Under Curve (AUC) exposure with the same dose due to variation of the clearance.
Patient A will experience drug induced adverse event due to an increased exposure to the drug. Patient C could have a treatment failure due to low exposition.
AUC: area under curve; C_p: plasma concentration of the drug; C_{max}: maximum plasma concentration; T_{max}: time to reach maximum concentration; $t_{1/2}$: terminal half-life

and if the AUC is too high, the drug could be more toxic. Modifications of bioavailability, volume of distribution or clearance have a direct impact on AUC (Fig. 2).

2.2. Volume of distribution and clearance

Two important pharmacokinetic variables are the volume of distribution and the clearance of the active substance. The volume of distribution (Vd) reflects the volume in which the drug is "virtually" diluted. It is not a physiological variable and might be higher than the body volume itself, if the drug has a high affinity for tissues. A drug which is very hydrophilic and stays in the plasma will have a Vd close to the intravascular total volume (5–8 L), whereas a drug which is very lipophilic will not stay in the plasma (which contains mostly water) and will have a much larger Vd. Sunitinib for example has a Vd which has been evaluated to 2230 L. Hydrophilicity or lipophilicity of a drug is its ability to be attracted by water or lipids respectively and depends on the polarity of the drug. It could be measured by the partition coefficient log P, which is the ratio of the amount of drug attracted by octanol

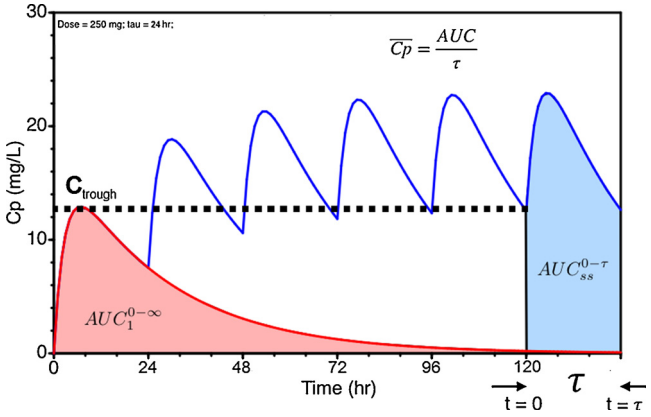

Fig. 3. Plasma concentration of a hypothetical drug given every tau hours.
C_{trough} at steady state (SS) can be used to estimate the AUC(0-τ) at steady state which reflects drug's exposure. Tau is 24 h in this example.
AUC: area under curve; C_p: plasma concentration of the drug; C_{max}: maximum plasma concentration; T_{max}: time to reach maximum concentration; $t_{1/2}$: terminal half-life

(lipid phase) or water.

Clearance reflects the volume of plasma cleared of the substance by amount of time. The half-life is the time needed to eliminate half of the drug from plasma. It depends on both clearance and Vd.

Precisely assessing AUC for each patient is not feasible in daily routine. Population pharmacokinetics through parametric or non-parametric modelling (Bayesian models) (Darwich et al., 2017) helps extrapolate the pharmacokinetic parameters from 2 measures, using probabilities to assess steady state AUC (Fig. 3).

3. General phenomenon involved in PKI's pharmacokinetics

3.1. Absorption

3.1.1. Pharmacokinetic principles of bioavailability

Most PKIs have a highly variable bioavailability (F). The bioavailability reflects the fraction of the parent substance that reaches the systemic blood compartment unchanged. Bioavailability differs among individuals because a drug which is taken orally has to go through several barriers. First in the intestine by passive or active re-uptake and then through the liver which might metabolise it before it gets into the main circulation in a process called hepatic first-pass effect.

The reference is always the intravenous injection. The absolute bioavailability is defined by the formula:

$$F = \frac{AUC_{(oral)}}{AUC_{(IV)}}$$

By definition, a drug given by the intravenous route will have an absolute bioavailability of 100%.

Bioavailability is a major source of interindividual pharmacokinetic variation (Hellriegel et al., 1996). Although there is no absolute threshold to define low or good bioavailability, a bioavailability under 30% is low, 30 to 70% moderate and over 70% considered good. When the average bioavailability of an active substance is high and close to 100%, there are very few interindividual variations. There is more AUC variability for drugs with low than with high bioavailability because low bioavailability implies several transport and/or metabolism steps preventing the parent compound from reaching the systemic circulation. Each of these transport and/or metabolism steps can have variable expressions, sometime genetically-determined, among subjects. Drugs with high bioavailability have little transport or metabolism after oral administration and therefore have less variable AUCs. Most PKIs have a low bioavailability: less than 30% (Klümpen et al., 2011).

Absorption also depends on the liposolubility of a drug. A

Table 1
Pharmacokinetic properties of approved protein kinase inhibitors in oncology.

TKI	Targets	Indication	Absorption		Distribution		Metabolism	Excretion	T ½
			F	Pic	Vd	Protein binding			
Afatinib	EGFR	EGFR + NSCLC	NA ↘	2-5h	4500L	95%	–	Biliary	37h
Alectinib	ALK	ALK + NSCLC	37% ↗	4-6h	475L	> 99%	Hepatic (CYP3A4)	Biliary	32h
Axitinib	VEGFR	RCC	58%	4h	160L	> 99%	Hepatic (CYP3A4)	Biliary/ Urinary	2,5-6h
Bosutinib	SRC, ABL	Ph + CML	NA ↗	6h	10 000L	96%	Hepatic (CYP3A4)	Biliary	34h
Cabozantinib	MET, VEGFR-2, RET	RCC, MTC	NA ↗	3-4h	319L	> 99%	Hepatic (CYP3A4)	Biliary/ Urinary	99h
Ceritinib	ALK	ALK + NSCLC	25% ↗	4-6h	NA	97%	Hepatic (CYP3A4)	Biliary/ Urinary	31-41h
Cobimetinib	MEK	BRAF V600 melanoma	46%	2,4h	800L	95%	Hepatic (CYP3A4 & UGT2 B7)	Biliary	44h
Crizotinib	ALK, MET, ROS1	ALK + NSCLC	43%	4-6h	1700L	91%	Hepatic (CYP3A4)	Biliary/ Urinary	42h
Dabrafenib	BRAF	BRAF V600 melanoma	95% ↘	2h	46L	99,7%	Hepatic (CYP3A4 & CUP2C8)	Biliary/ Urinary	8-10h
Dasatinib	BCR-ABL, c-KIT, PDFR-β, SRC	Ph + CML, Ph + ALL	80%	0,5 – 3h	2500 L	96%	Hepatic (CYP3A4)	Biliary/ Urinary	3-6h
Erlotinib	EGFR	EGFR + NSCLC, PC	59% ↗	4h	232L	95%	Hepatic (CYP3A4 & CYP 1A2)	Biliary	36h
Gefitinib	EGFR	EGFR + NSCLC	59%	3-7h	1400L	90%	Hepatic (CYP3A4 & CYP2D6)	Biliary	42h
Imatinib	BCR-ABL, c-KIT, PDGFR-α	GIST, CML, ALL, dermatofibrosarcoma protuberans	98%	2-4h	295-590L	95%	Hepatic (CYP3A4/5)	Biliary/Urinary	18-22h
Lapatinib	HER2, EGFR	HER2+ breast cancer	NA ↗	4h	2200L	99%	Hepatic (CYP3A4)	Biliary	24h
Lenvatinib	VEGFR, FGFR,	Iodine refractory thyroid carcinoma	70-85%	1-4h	43-121L	98,5%	Hepatic (CYP3A4)	Biliary/ Urinary	28h
Nilotinib	BCR-ABL, c-KIT	Ph + CML	30% ↗	2-4h	579-800L	98%	Hepatic (CYP3A4)	BIliary	17h
Osimertinib	EGFR T790M	EGFR T790 M NSCLC	NA	6h	986L	High	Hepatic (CYP3A4)	Biliary/ Urinary	48h
Palbociclib	CDK 4/6	RH + breast bancer	46%	6-12h	NA	85%	Hepatic (CYP3A4 & SULT2A1)	Biliary/Urinary	28h
Pazopanib	VEGFR, c-KIT	RCC, GIST	14-39% ↗	2-4h	9-13L	99%	Hepatic (CYP3A4)	Biliary	30h
Regorafenib	VEGFR, PDGFR-β, RAF, FLT-3, c-Kit, Ang-2	CRC, HCC, (Ewing sarcoma)	< 70% ↗	4h	76L	99,5%	Hepatic (CYP3A4 & UGT1A9)	Biliary/ Urinary	20-30h
Sorafenib	VEGFR, RAF, FLT-3, c-Kit	RCC, HCC, non-medullary thyroid carcinoma	39-49% ↘	2-6h	213-400L	99,5%	Hepatic (CYP3A4 & UGT1A9)	Biliary/ Urinary	25-48h
Sunitinib	VEGFR, c-KIT	RCC, GIST, p-NET	NA	6-12h	2230L	95%	Hepatic (CYP3A4)	Biliary/ Urinary	40-60h
Trametinib	MEK	BRAF V600 melanoma	72% ↘	1,5h	1200L	97%	Carboxylesterases	Biliary/ Urinary	5,3d
Vandetanib	EGFR, VEGFR-2, RET	MTC	NA	4-10h	7500L	94%	Hepatic (CYP3A4)	Biliary/ Urinary	19d
Vemurafenib	BRAF	BRAF V600 melanoma	NA ↗	4h	90L	99%	Hepatic (CYP3A4)	Biliary	50h

↗: Absorption increased with meals; ↘: absorption decreased with meals.
CRC: ColoRectal Cancer; F: biodisponibilité; GIST: Gastro-Intestinal Stromal Tumor; HCC: Hepato-cellular Carcinoma; HR: hormone receptor MTC: Medullary Thyroid Cancer; NSCLC: Non-Small Cell Lung Cancer; PC: Pancreatic Cancer; p-NET: pancreatic NeuroEndocrine Tumor; RCC: Renal Cell carcinoma; T ½: half-life; Vd: distribution volume.

liposoluble drug crosses different membranes with passive diffusion, whereas hydrophilic drugs, which are polarised, have a lower absorption rate through the epithelium of the gastro-intestinal tract. We summarised key pharmacological parameters in Table 1.

3.1.2. Saturable absorption

Absorption can happen through 2 different mechanisms: passive diffusion or active transport. Active transporters are saturable. When the given dosage is too high, the transporters cannot re-uptake all the drug, resulting in a decreased global bioavailability. For example, the AUC of sorafenib is almost the same with a dose of 800 mg per intake or with a dose of 1600 mg per intake, because of saturable absorption (Hornecker et al., 2012). As a consequence, 400 mg 3 times a day gives a higher AUC than 800 mg twice a day. Pazopanib also has a saturable absorption. According to Yu & colleagues (Yu et al., 2016), switching from 800 once daily to 400 mg twice daily could increase AUC by 59% (model-based simulations)

Splitting the dose of a drug could increase more efficiently the AUC than increasing a single dose per day.

3.1.3. Gastric surgery

Weak acids are absorbed in the acidic stomach. Gastrectomy could decrease the absorption of weak acids, when pKa, which is the negative base-10 logarithm of the acid dissociation constant (Ka) of a solution, is between 2 and 6.

Major gastric surgery decreases the bioavailability of nilotinib in the treatment of GastroIntestinal Stromal Tumours (GIST) (Kim et al., 2011). Nilotinib, which has 2 acid groups, has two pKa: one at 2.1 and one at 5.4. Thus, nilotinib might exist in 3 forms in the gastro-intestinal tract. In its acid form, nilotinib has no charge, and is therefore lipophilic and able to go through membranes by passive diffusion. However, the basic form of nilotinib is charged. When the pH increases above 5.4, nilotinib molecules are becoming more hydrophilic and have a lower ability to cross cell membranes. This can be extrapolated to other PKIs with a PKa between 2 and 6: pH can affect PKI's absorption, which explains why patients with major gastrectomy might not be able to absorb some PKIs.

This has also been shown in 2 case reports of obese patients treated with 400 mg OD imatinib who underwent a sleeve gastrectomy (Liu and Artz, 2011; Pavlovsky et al., 2009). One had a 2 fold decrease of imatinib plasma concentration after sleeve gastrectomy (1558 ng/mL before and 629–836 ng/mL after) and the other 6 fold (965 ng/mL before and 166 ng/mL after).

Gastrectomised patients might have a very different bioavailability, and whenever relevant, these patients could be followed by therapeutic drug monitoring.

3.1.4. Role of proton pump inhibitors and anti-acids

Anti-acids and particularly proton pump inhibitors (PPI) are widely used in the cancer population, with a prevalence of 20%–55 % depending on the cancer type (Budha et al., 2012). Esomeprazole and other PPI increase average gastric pH affecting PKI's absorption.

Pazopanib for example, has shown a very low bioavailability in patients receiving concomitant esomeprazole, for similar reasons than nilotinib (cf. supra). Pazopanib is highly liposoluble at pH 1.0 and is showing a very low liposolubility and bioavailability above a pH of 4.0 (Tan et al., 2013). Patients treated by sunitinib for metastatic renal Clear Cell Carcinoma (mRCC) have a significant decrease in overall survival when treated with PPI or ranitidine (Ha et al., 2015). Nilotinib has a 34% decrease in AUC with concomitant use of omeprazole (Yin et al., 2010). Kletz & al (Kletzl et al., 2015) estimated that erlotinib AUC is divided by 2 with concomitant omeprazole. Staggered ranitidine, i.e. 150 mg twice daily of ranitidine with erlotinib given 10 h after the previous evening dose and 2 h before the next ranitidine morning dose, resulted in an erlotinib exposure decrease of approximately 15%.

Van Leeuwen & al (van Leeuwen et al., 2014) reviewed some of these interactions and recommend that crizotinib, dasatinib, erlotinib, gefitinib and lapatinib should not be associated with PPI and crizotinib, dasatinib and gefitinib should not be associated with anti-H2.

Acidic beverage could replace gastric acidity: patients treated with erlotinib and concomitant proton pump inhibitors had their bioavailability significantly increased (+39%, P = .004) by taking the treatment with cola when compared to erlotinib taken with water (van Leeuwen et al., 2016).

Whenever a drug's absorption relies on gastric acidity (cf. supra) direct anti-acid should be given at least 4 h before or 2 h after the drug intake. PPI and anti-H2 should be avoided whenever possible and PPI and anti-H2 should always be taken at least 2 h after the PKI or 10 h before, in order to have a normal gastric pH whenever the drug is taken. When PPI could not be avoided, concomitant dosing of the drug with cola could be considered.

3.1.5. Food

The pH of the stomach is around 1.2 during sleep, while it is around 3.5 after a meal. A meal also alters gastric emptying, which is delayed by the secretion of cholecystokinin in the duodenum when lipids and proteins leave the stomach. Bioavailability of a drug taken fed raises a problem of intra-individual variation, because patients have very diverse diets, especially regarding the amount of fat. Fat intakes notably slow digestion speed, and could increase the absorption of lipophilic drugs Therefore, pazopanib administered with food shows a twofold higher exposure compared to fasted (fed/fasted ratio which is the ratio of the AUC fed under the AUC fasted) (Verheijen et al., 2016). Lapatinib presents a fed/fasted ratio of around 4.1 (Kang and Ratain, 2010).

Some PKIs have been developed fed and some other fasted. The modality of administration should be explained to the patient before initiation of the oral treatment. Patients are considered fasting for oral drugs when the drug intake is at least one hour before or two hours after the ingestion of food. Patients with unexpected toxicity or no side effects should be asked their schedule of drug and food intakes.

3.1.6. Role of transporters

Permeability-glycoprotein (P-gp), also known as multidrug resistance protein 1 (MDR1) or ATP-binding cassette sub-family B member 1 (ABCB1), is an efflux pump with a very large spectrum of activity, present in various endothelium: liver, jejunum, or in brain capillary endothelial cell among others. P-gp notably plays a role in the blood brain barrier to protect the neurones from xenobiotics. ABCG2 (ATP Binding Cassette subfamily G member 2), also known as BCRP (Breast Cancer Resistant Protein) has a similar role. As a mechanism of resistance, P-gp can be overexpressed by cancer cells, pumping out of the cell the drug that is active intracellularly.

Some PKIs are known as substrates, activators or inhibitors of P-gp activity, impacting their own absorption. Imatinib for example, is an ABCG2 substrate and activator. Imatinib exposure decreases when given chronically with the same dosage: imatinib increases the expression of intestinal efflux pump, decreasing its absorption over time (Judson et al., 2005). In vitro, Caco-2 cells (model of gut wall cells) exposed to imatinib increase the expression of ABCG2 and, to a lesser extent, P-gp (Burger et al., 2005). A similar phenomenon has been demonstrated for sorafenib when chronic drug intake reduces drug exposure (Arrondeau et al., 2012) in patients treated for a metastatic hepatocellular carcinoma.

As a consequence, chronic exposure to a PKI could change its own bioavailability (and clearance). Clinicians should be aware that better tolerance and decreased efficacy of a treatment by PKI on the long term could be due to lower exposure, and could be therefore an indication of PKI dose increase or drug monitoring.

3.1.7. Time of the day

Enzymes and transporters involved in the pharmacokinetics of drugs, such as CYP3A4 and ABCB1, have time-dependent variations in

expression which may have profound effect on the exposure to several drugs. Kloth & al (Kloth et al., 2015) found that sunitinib trough plasma concentrations were significantly lower when patients were administered sunitinib in the morning, than at noon or in the evening. However, AUC was not significantly different when sunitinib was administered at different time of the day. The difference in sunitinib trough concentrations may be attributed to daily changes in elimination. A study conducted in rabbit showed that sunitib Cmax more than doubled and AUC increased by 64% in rabbits that were given the drug at 20:00 instead of 8:00 (Szałek et al., 2014).

Although the chronobiology of PKI's pharmacokinetics remains poorly explored, patients should be advised to take their PKIs at the same clock time of the day.

3.1.8. Adherence

Jabbour & al (Jabbour et al., 2012) classified the causes of non-adherence into 3 categories:

- Treatment: side effects, cost, complexity of treatment regimen, concomitant medication, lack of immediate benefit.
- Patient: lack of understanding of the treatment and the disease, psychological factors, poor literacy, lack of support system, religious/cultural belief, physical difficulties, age under 40 or older than 75 yrs.
- Health care provider: lack of relationship or poor communication with the prescriber, fragmented health care system, failure to select patient for oral therapy

This might result in either a loss of drug efficacy or increased toxicity (if the patient tries to compensate a missed intake by taking several doses of the drug in one intake) (McCue et al., 2014).

Several interventions might improve adherence. A good communication and therapeutic education of the patient, including the explanation of the expected or possible adverse events and their management is essential. It is also important to simplify prescriptions as much as possible. Other healthcare professionals might also help: pharmacists play an important role detecting important adverse effects, providing therapeutic education and giving practical recommendations especially regarding drug administration. The DRug Adherence Work-up (DRAW) (Doucette et al., 2012) tool might help them. Other professionals, such as nurses, might also help improve treatment adherence. Particular attention should be paid to patients after 75 years (Marcum et al., 2017), and the use of mind reminder tools, like smartphone apps (Dayer et al., 2013), might help this category of patients.

It should never be assumed that patient comply to the treatment. A patient with no side effects should be questioned on treatment observance. TDM could help in the diagnosis of poor compliance.

3.1.9. Other sources of variation

Gut motility might also be a factor of variability. Using parasympatholytics or mimetics can change drug absorption. Metoclopramide for example, increases gastric emptying, and could be a source of pharmacokinetic change (Greiff and Rowbotham, 1994). There is no clinical proof yet that such an effect could increase the toxicity of PKIs, but this should be borne in mind. The available surface of the gut also plays a role. A normal intestine has a surface of absorption of around 200m^2. Therefore, patients having important digestive surgeries should be closely monitored.

3.2. Distribution

3.2.1. PK principles

Depending on their affinity for tissues, proteins or lipids, different drugs have different distributions into the body as reflected by the volume of distribution. For example sunitinib has a Vd of approximately 2500 L.

3.2.2. Protein binding

PKIs are extensively protein-bound to albumin (about 95%) and, to a lesser extent, to α1-acid glycoprotein. Only the free part of the drug is active, and the equilibrium between bound and free drug is reversible and follows the law of mass action. Although only unbound drug is active, albumin concentration rarely influences drug exposure. Lower albumin concentrations decrease the bonded fraction of the drug, which makes the effective concentration higher, but this effect is balanced by a higher clearance of the drug (if the drug elimination processes are not saturable).

Sorafenib is a highly bound kinase inhibitor, with > 99.5% bound to plasma proteins, mainly albumin. Although the clearance is increased when albumin is low (Tod et al., 2011), there is no evidence that it affects directly the exposure to the drug. However, albuminemia also reflects sarcopenia (Visser et al., 2005) which is a known factor of poor tolerance to PKIs (see below). For similar reasons α1-acid glycoprotein, whose concentration increase during inflammation, is unlikely to change drug exposure significantly (Israili and Dayton, 2001).

3.2.3. Role of sarcopenia

Sarcopenic patients, who have a low muscle mass, have a higher risk of toxicity when treated with sunitinib for mRCC or sorafenib for HCC and mRCC (Antoun et al., 2010; Huillard et al., 2013). Patients with sarcopenia would have high intra-tissular exposure to unbound PKI. They have an increased propensity for nosocomial infections and other complications, which possibly reflects a global frailty and a vulnerability to PKI adverse events.

Sarcopenia is not necessarily correlated to body mass index (BMI), and obese patients can be sarcopenic, which makes clinical diagnosis difficult. Standardised techniques have been developed to assess sarcopenia which can for example be appraised by measuring area of muscle of the cross section of the third lumbar vertebra (Antoun et al., 2010). This method is reproducible and might be automatized. The combination of sarcopenia as assessed below and a BMI < 25 is a good predictor of a PKI's toxicity.

Sarcopenic patients are more sensitive to PKIs toxicity and should be clinically monitored more thoroughly.

3.2.4. Role of obesity

The proportion of fat tissue might have a big impact on the volume of distribution. Fat proportion might range from 10% in malnutrition to 50% for obese patients. Lipophilic substances then have a larger volume of distribution and consequently a lower clearance. Bioavailability is also increased (Brill et al., 2014), possibly due to obesity-induced suppression of CYP3A activity (Brill et al., 2015; van Rongen et al., 2018).

Very few cases have been reported of PKI treatments among obese patients.

Desar & al [27] reported the case of a patient treated with sunitinib for a GIST having a BMI of 47 kg/m^2 treated with 50 mg of sunitinib per day. The steady-state concentrations reported were 20–25 ng/mL, which is roughly 70% less than the average exposure reported in the literature. Pavlovsky & al (Pavlovsky et al., 2009) reported the case of an obese patient treated by 400 mg of imatinib per day for a CML, who had normal plasma exposure (1558 ng/mL, higher than the mean exposure concentration i.e. 1000 ng/mL). Liu et al described a patient who had a sleeve surgery and (Liu and Artz, 2011) a BMI of 50. She was initially treated with 400 mg of imatinib per day, and showed partial response with 35% of Chromosome Philadelphia in bone marrow (95% of chromosome Phi + at diagnosis). After doubling the dosage, the patient had a complete response (0% of chromosome Phi + in bone marrow sample), but had important adverse effects. This example illustrates the risk of underdosing an obese patient.

Obese patients are a category of patients who need a closer

attention. Whenever no adverse effects are seen, dose could be increased and TDM could help to reach an efficient dose.

3.2.5. Blood-brain barrier, leptomeningeal and brain metastases

3.2.5.1. The blood-brain barrier. The brain is protected from xenobiotics by the blood-brain barrier (BBB). The efflux pumps P-gp (ABCB1) and ABCG2 (BCRP), reject substrate drugs into the plasma when they reach the cytoplasm of BBB endothelial cells. Drugs with high liposolubility, allowing passive diffusion, and with a low molecular mass can cross the BBB if they are not substrates of P-gp or ABCG2.

3.2.5.2. Brain metastases. The ability to cross BBB could play an important role for anti-cancer drugs. Crizotinib, a selective inhibitor of the anaplastic lymphoma kinase (ALK), is highly active in EML4/ALK translocated lung adenocarcinoma. Crizotinib has a low diffusion into healthy brain, with a cerebrospinal fluid (CSF)-to-plasma ratio of 0.0026 (Costa et al., 2011). New therapies i.e. ALK inhibitors of third generation, have a better ability to cross the BBB, allowing the treatment of brain metastasis resistant to crizotinib. Alectinib and brigatinib, two third generation ALK inhibitors, are associated with better response rates of central nervous system (CNS) lesions compared to crizotinib (78% with brigatinib, 81% with alectinib, compared to 29–50% with crizotinib (Camidge et al., 2018; Peters et al., 2017)). Similar results have been reported with osimertinib in EGFR-mutated lung cancer (Reungwetwattana et al., 2018) (objective CNS response rate of 91% with osimertinib vs. 68% with standard anti-EGFR therapy).

The vascularization of brain metastases, and its permeability, could differ from the healthy vessels which protects the CNS (Wang et al., 2017). Most PKIs are substrates of both P-gp and BCRP and have a poor diffusion into the cerebrospinal fluid (CSF) (Choo et al., 2014; Kim et al., 2012; Mittapalli et al., 2013; Mittapalli et al., 2012; Oberoi et al., 2013; Vaidhyanathan et al., 2014). A drug which is not able to cross the BBB could nevertheless have an activity if the permeability of the tumour vessels is high enough. Carbon-11 radiolabeled lapatinib could penetrate into brain metastasis, although it does not diffuse into normal brain (Saleem et al., 2012). However, 2 phase II studies of lapatinib in HER2+ breast cancer with brain metastases had poor CNS lesion response (˜5%) (Lin et al., 2009, 2008).

Concomitant radiotherapy is a way to create a breach (Zhang et al., 2014) in the BBB, thus allowing a better diffusion in the CSF and brain metastasis. A meta-analysis conducted by Zheng et al. (Zheng et al., 2016) reviewed the association of whole brain radiotherapy (WBRT) alone or with erlotinib/gefitinib in brain metastatic lung cancer with a wild type or a mutated EGFR profile. WBRT combined with gefitinib/erlotinib significantly increased CNS response rate (OR = 2.16, 95% CI: 1.35–3.47; P = 0.001) and prolonged 1-year survival rate compared to WBRT alone (OR = 2.43, 95% CI: 1.51–3.91; P = 0.0002). EGFR status was unknown for most analysed studies.

Most PKIs have a low CSF concentration, due to the fact that most of them are substrate of both P-gp and BCRP. Although the ratio of CSF/plasma concentration is not an absolute surrogate to predict PKIs activity against a brain metastasis, PKIs BBB diffusion should always be considered for the treatment of any cancer with a brain lesion.

3.2.5.3. Leptomeningeal carcinomatosis (LMC). Small leptomeningeal lesions are poorly connected to the systemic vasculature, and the cancer cell exposure to treatment relies only on the ability of the drug to diffuse through the BBB. The concentration in the CSF and penetration rate of gefitinib in the CSF of patients are 8.2 nM (± 4.3 nM) and 1.1% while the concentration and penetration rate of erlotinib in the CSF are 66.9 nM (± 39.0 nM) and 2.8% (Togashi et al., 2012). Erlotinib thus exhibits a better brain diffusion than gefinitib. Lee & al, confirmed this effect clinically [31]: in a retrospective analysis, 9 of 14 patients treated with erlotinib converted to negative cytology compared to 1 of 11 treated with gefitinib, (64% vs 9%, p = 0.012).

Reinwald &al (Reinwald et al., 2014) studied nilotinib CSF concentration and measured a ratio of CSF/plasma concentration of 0.0053. However, nilotinib in the treatment of BCR-ABL leukaemia with CNS lesions was shown to be effective in the brain. An explanation would be the high protein binding affinity of this drug and the absence of albumin in CSF allowing the unbound concentration of the drug in the CNS to be high enough to be effective.

Efflux pump polymorphism also has an impact on CSF diffusion. Patients with the deficient ABCG2 421C > A allele have a significantly higher erlotinib CSF penetration (Fukudo et al., 2013).

High doses could theoretically allow saturating P-gp and BCRP efflux pump and increase CSF diffusion. Pulsatile methods, i.e. weekly administration of large intakes, have been proposed for patients with leptomeningeal disease of EGFR-mutated lung adenocarcinoma. Case reports of 1000–1500 mg in one intake per week, in addition to radiotherapy led to manageable toxicities and disease stabilisation (Clarke et al., 2010). A phase 1 study of erlotinib at 2000 mg weekly showed similar results (Milton et al., 2006).

New generation EGFR inhibitors such as osimertinib which has a good brain diffusion profile should be preferred whenever possible in EGFR-mutated NSCLC (Nanjo et al., 2018; Planchard, 2017; Sakai et al., 2017; Yang et al., 2017).

3.3. Metabolism / elimination

3.3.1. PK principles

Most PKIs are too hydrophobic in their active form to be eliminated through the glomeruli and excreted in urine: they require prior metabolisation before hepatic or renal elimination.

There are 2 types of metabolisations which transform lipophilic drugs into more hydrophilic metabolite(s):

- Phase I metabolism via cytochromes (CYP450). There are more than 50 cytochrome P450 enzymes, but six of them metabolise 90 percent of drugs, with the two most significant enzymes being CYP3A4 and CYP2C. This process includes oxidation, but not only. Reduction and hydrolysis or cyclisation might also occur.
- Phase II metabolism via conjugation reactions. Glucuronidation, the transfer of a glucide, is an important mechanism and occurs via Uridine 5′-diphospho-glucuronosyltransferase (UDP-glucuronyltransferase). Other mechanisms include: glutathione conjugation, methylation, acetylation or sulfonation.

Cytochromes are found in many organs (skin, kidney, gut wall, lungs) but most of CYP-dependent metabolism occurs in the liver.

3.3.2. Cytochromes mediated drug-drug interaction (DDI)

Cytochrome P450 enzymes can be inhibited or induced by drugs, resulting in clinically significant drug-drug interactions that can cause unanticipated adverse reactions or therapeutic failures. Antiepileptic or antiretroviral treatments are known to interact with CYP3A4 which is the main metabolic pathway of most PKIs (Table 1).

Other interactions are less expected : glucocorticoids are widely used and they induce the expression of CYP3A4 (El-Sankary et al., 2002). Similarly, inflammation, via interleukine-6 (Robertson et al., 2008a), inhibits the expression of CYP3A4, and could lead to excessive drug toxicity caused by reduced CYP3A4-mediated metabolism (Robertson et al., 2008b). Although there is no proof of an increased toxicity in patients treated by PKIs, patients having CRP > 10 mg/L or **α**1-acid glycoprotein level > 1.5 g/L have 3 times more non-haematological complications, when treated by docetaxel, which is mainly eliminated by CYP3A4 (Charles et al., 2006).

Fenofibrate, which is a widely prescribed drug for triglyceride reduction, is also a potent CYP3A4 inducer. Mir&al (Mir et al., 2011) showed that the progression of a patient treated by erlotinib for a lung adenocarcinoma with an EGFR mutation and treated with concomitant

fenofibrate, exhibited a serum plasma concentration half of the lower normal limit. Doubling erlotinib intakes restored plasma concentration of erlotinib and drug efficacy with a partial response. Approximately 50% of patients treated with everolimus exhibit hypertriglyceridemia which is often treated with fenofibrate, a CYP3A4 inducer. Mir & al (Mir et al., 2015) reported a case of a patient treated by everolimus who developed grade 2 stomatitis and grade 2 hypertriglyceridemia. When fenofibrate was started, everolimus concentration dropped from 10.1 ng/mL to 4.2 ng/mL, and both adverse events disappeared. Fenofibrate was discontinued and the plasma concentration of everolimus later normalised.

Mitotane, a drug used in adrenocortical carcinoma, is one of the most powerful CYP 3A4 inducer known. It also has a very high lipophilicity and thus a very long half-life (18–159 days) (van Erp et al., 2011). Sunitinib has been used for the treatment of adrenocortical carcinoma (Kroiss et al., 2012). Patients primarily treated with mitotane had worse outcomes and their sunitinib plasma concentrations were almost 10 fold lower than mitotane-naïve patients. This effect on CYP 3A4, due to mitotane's very long half-life, might last more than 3 months, compromising most second line treatment in this disease.

More generally, any drug that alters CYP3A4 activity should be suspected of causing drug interactions when a concomitant treatment with a PKI is started.

3.3.3. Food and herb-drug interactions

Grapefruit and Saint-John's Wort are well known to respectively inhibit and induce CYP3A4. We summarised in Table 2 other clinically relevant her or food CYP3A4 inhibitors or inducers (no in vitro or animal model was considered) which should be avoided concomitantly to PKIs.

Food habits and phytotherapy intakes should always be investigated before the initiation of a PKI and when high grade toxicity or no adverse event is seen. Most interactions between phytotherapy and CYP3A4 have poorly been explored and phytotherapy-induced interaction should always be considered.

3.3.4. Glucuronidation, UGT

5′-diphospho-glucuronosyltransferase (UDP-glucuronyl-transferase) also called UGT, has a well-known importance for the metabolism of SN-38, the active metabolite of irinotecan, a camptothecin derivative. UGT1A1 polymorphism predicts severe toxicity (deficiency is known as Gilbert' syndrome). UGT is an enzyme which transfers a glucose derivative on xenobiotics, making them more hydrophilic.

Like cytochromes, there are different families of UGT. UGT1A9 has a demonstrated role in sorafenib metabolisation. However, no major role of UGT1A9 polymorphism on sorafenib exposure has been clearly demonstrated so far (Boudou-Rouquette et al., 2012). Similarly, no drug-drug interactions from glucuronidation mechanism have been clearly identified with PKIs.

3.3.5. ABC transporters

ABC transporters (ATP-Binding Cassette), play an important role in the bioavailability, the BBB, and the detoxification of drugs. Both P-gp (ABCG1) and ABCG2 (BCRP) were originally discovered as being responsible for some Multi-Drug Resistance cancer cell phenotype. Durmus & al (Durmus et al., 2015) reviewed the role of these transporters in multi-kinase inhibitors: most of them are substrate of both P-gp and ABCG2.

Interestingly, some multi-kinase inhibitors also inhibit ABC transporters. Imatinib, for example, is a potent ABCG2 inhibitors (He and Wei, 2012), and reverses some in vitro MDR phenotypes.

A role of proton pump inhibitors on P-gp and PKI drug-drug interaction should also be expected (cf. supra). Afatinib, which is mainly eliminated without transformation via P-gp (Wind et al., 2017). However, rifampicin, a known powerful P-gp modulator, had no clinically relevant effect on afatinib exposure (Wind et al., 2014). Clinically significant transporter mediated interactions with PKIs are unlikely.

3.3.6. Role of genetic polymorphism

Some cytochromes, such as CYP2D6, are highly polymorphic, dividing patients between poor metaboliser, intermediate metaboliser, extensive metaboliser, or ultra-extensive metaboliser. These polymorphisms can have a direct impact on therapeutic response as was shown with tamoxifen (Borges et al., 2006). Same variations could occur through ABC transporters protein and the UGT. The impact of pharmacogenetics on cytotoxic treatment is now well established (Deenen et al., 2011). Similarly, forty-nine single nucleotide polymorphisms (SNPs) involved in the pharmacokinetic and pharmacodynamic pathway of sunitinib were associated with progression-free survival (PFS) and overall survival (OS) in 127 patients with advanced GIST treated with sunitinib (Kloth et al., 2018, p. 201). Similar results were found for genetic polymorphisms related to angiogenesis which modified outcomes of patients with GIST treated with imatinib (Verboom et al., 2017).

However, no study has demonstrated the role of pharmacogenomics to improve efficiency and safety of PKIs in daily routine.

3.3.7. Role of tobacco

Tobacco's polycyclic aromatic hydrocarbons can induce CYP 1A2, CYP 1A1 and CYP 2E1 (Zevin and Benowitz, 1999). EGFR-mutated lung cancers are more common in the "never smoker population". However, some of them smoke. The pharmacokinetics of erlotinib, a PKI specific

Table 2

Herbs or food with clinically relevant known interactions with CYP3A4 probes (either induction or inhibition). Concomitant use of these complementary alternative medicine or diet can lead to increased toxicity (CYP3A4 inhibition) or decreased efficiency (CYP3A4 induction) and is strongly discouraged for most PKIs.

CYP3A4 Inhibitor	CYP3A4 Inductors
Cranberry (*Vaccinium Macrocarpon*) (Ngo et al., 2009)	Echinacea (*Echinacea Purpurea*) (Gorski et al., 2004; Penzak et al., 2010)
Green tea (*Camellia Sinensis*) (Chow et al., 2006)	Ginseng (*Panax Ginseng*) (Malati et al., 2012)
Goldenseal (*Hydrastis Canadensis*) (Gurley et al., 2008, 2005; Xin et al., 2006)	Licorice (*Glycyrrhiza Glabra*) (Tu et al., 2010)
Lime (*Citrus Arantifolia*) (Bailey et al., 2003)	Ginkgo (*Ginkgo Biloba*) (Markowitz et al., 2003; Uchida et al., 2006)
Pomelo (*Citrus Maxima*) (Grenier et al., 2006)	Saint-John's wort (*Hypericum Perforatum*) (Markowitz et al., 2000)
Grapefruit (*Citrus Paradisi*) (Edgar et al., 1992)	Soy extracts (*Glycine max*)/ genistein (Xiao et al., 2012)
Sevilla orange (*Citrus Aurantium*) (Di Marco et al., 2002; Lemahieu et al., 2003)	
Peppermint (*Mentha Piperita*) (Dresser et al., 2002; Gelal et al., 2005)	
Black seed (*Nigella Sativa*) (Al-Jenoobi et al., 2010)	
Wuzhi (*Schisandra Sphenanthera*) (Jiang et al., 2010; Xin et al., 2009)	
Broccoli sprouts extracts /kale/sulforaphane (Poulton et al., 2013)	
Quercetin (Duan et al., 2012)	
Vitamin E (Bárány et al., 2001)	
Resveratrol (Bedada and Nearati, 2015; Chow et al., 2010)	
Piperin / pepper extracts (*Piper Nigrum*) (Rezaee et al., 2014)	

of EGFR mutation, is influenced by smoking. Erlotinib is mainly eliminated by CYP 1A2 and CYP 3A4 and shows an approximately 2 fold decreased exposure in the plasma of smoking patients (Hamilton et al., 2006). Hughes &al (Hughes et al., 2009) proposed to double the dosage from 150 to 300 mg per day for patients smoking more than 10 cigarettes per day, restoring erlotinib activity.

Imatinib is partially metabolised by CYP1A2. Although smoking has not proved to significantly change the pharmacokinetics of imatinib (van Erp et al., 2008), non-smoking patients treated with imatinib for a GIST have a trend to respond better (PFS) than smokers (p = 0.052).

Patients treated with erlotinib should be encouraged to quit smoking. When it is not possible, alternative treatments (gefitinib, afatinib or even osimertinib) should be preferred, or erlotinib doses can be doubled and plasma concentrations monitored.

3.3.8. Hepatic failure

PKIs mainly have biliary elimination. Sorafenib, mostly metabolised by CYP3A4 and UGT1A9, has first been approved for the treatment of hepatocellular carcinoma (Bruix et al., 2017; Llovet et al., 2008). Most patients with hepatocellular carcinoma have cirrhosis, and thus an impaired hepatic function. Non-cancerous hepatic tissue of patients having a HCC has a 4 to 10-fold lowered cytochrome P-450 activity per gram of liver (Ye et al., 2014). Nevertheless, the recommended starting dose of sorafenib was found to be the same in hepatocellular carcinoma than in clear renal cell carcinoma or other solid cancer i.e. 400 mg b.i.d. (Strumberg et al., 2007), with no substantial PK difference between Child-Pugh A and Child-Pugh B patients in a phase 2 study (Abou-Alfa et al., 2006). Similarly, imatinib pharmacokinetic properties were not altered in a phase I study in patients with HCC (Treiber et al., 2008). Two case reports did not show an increased toxicity with imatinib in GIST patients with cholestasis and impaired hepatic function (Bauer et al., 2002). A phase 1 study was conducted with sorafenib in patients with altered hepatic function (Miller et al., 2009). The authors recommended to lower sorafenib initial doses when bilirubinemia is > 3x ULN or if albuminemia is < 25 g/L, which *reflects the severity of liver dysfunction*. Another phase 1 study conducted in patients receiving erlotinib (Miller et al., 2007) showed that patients with AST > 3xULN or bilirubin > 1 mg/dL or albuminemia < 25 g/L should be treated with half-dose, due to a 2 to 3-fold lower clearance in this population.

Pazopanib was also evaluated in a phase 1 study among patients having a liver dysfunction (Shibata et al., 2013) and treated for a solid cancer. Patients having a mild hepatic impairment (total bilirubin > upper limit normal (ULN) to 1.5 x ULN or AST > ULN, according to the National Cancer Institute Organ Dysfunction Working Group) exhibited normal toxicity and pharmacokinetics and should be treated like other patients. Patients having a moderate or severe dysfunction according to the same criteria had both a MTD of 200 mg per day, although having a much lower plasma concentration of Pazopanib.

All these authors recommend that in case of moderate or severe dysfunction (Child-Pugh B or C), the drug should be started at lower dose and an early drug monitoring should be performed.

3.3.9. Renal failure

PKIs are too hydrophobic to be directly eliminated in the urine. Only hydrophilic metabolites, often inactive, are excreted by renal route. Thus, renal impairment has a very low impact on kinase inhibitors toxicity. As an example, erlotinib and sorafenib clearance do not differ in patients with renal dysfunction (studies limited to GFR > 20 mL/min/1,73m^2) and patients with normal renal function [70].

Sunitinib is not dialyzable (Izzedine et al., 2009; Janus et al., 2012). Yet, a phase 1 study (Khosravan et al., 2010) showed a lower maximum plasma concentration of sunitib among hemodialysed patients, possibly due to a diminution of the bioavailability of the drug (unknown mechanism). Severe renal impairment (GFR < 30 mL/min) did not influence the pharmacokinetics of sunitinib administered as a single 50 mg dose. Sunitinib, temsirolimus, everolimus and pazopanib, in small cohorts of patients treated for mRCC and hemodialysed seemed to have a similar toxicity profile. However, severe adverse events due to cardiovascular complications were also reported (Kennoki et al., 2011; Masini et al., 2012; Shetty et al., 2014). Sorafenib AUC increased in hemodialysed patients (Hilger et al., 2009) and initial drug dose should be decreased and plasma concentrations monitored.

Erlotinib gefitinib, afatinib, nilotinib and imatinib display a safe profile of use among hemodialysed patients in case series (Bersanelli et al., 2014; Janus et al., 2012; Onaka et al., 2012; Togashi et al., 2010).

Anti-angiogenics PKIs can cause serious cardio-vascular side effects and patients with renal failure or requiring hemodialysis should be treated with more caution (start with lower dose) and closely monitored clinically. Janus et al. reviewed the use of PKIs (Janus et al., 2012) and recommend that they should be administered post dialysis, since the dialysability of these drugs is most of the time unknown.

4. PK/PD relationships and Impact of Therapeutic Drug Monitoring (TDM)

4.1. Therapeutic index

Correct exposure to a PKI with adequate AUC is required for the treatment to be efficient and not too toxic. Most PKIs are prescribed at a flat dose, despite a high inter-patient variability and a narrow therapeutic index. Many patients fail to reach an appropriate exposure, and thus might experience treatment failure. In its recommendation for prescription, only axitinib proposes an increase of its dosage in case of good tolerance (which was originally proposed in the phase 3 study), lowering the chances of underdosing the patient. Drug monitoring is suitable for drugs satisfying certain criteria (Ghiculescu, 2008) such as a narrow therapeutic index, significant pharmacokinetic variability, a significant relationship between plasma concentration and clinical effects, and an available cost-effective drug assay.

Most antiangiogenic PKIs prescribed in oncology have a wide kinase spectrum activity and inhibit kinase that could be responsible for off-target effects (Gougis et al., 2017). Therefore the efficacy dose is close to the toxic dose and they have a narrow therapeutic index. For sunitinib, among others, toxicity could also be a surrogate of efficacy. In clear cell renal cell carcinoma patients treated with sunitinib, hypertension (Izzedine et al., 2015) or hypothyroidism (Schmidinger et al., 2011) correlate with better outcome. For these PKIs, exposure is correlated to efficacy (Hayato et al., 2018; Houk et al., 2010; Lacy et al., 2018; Solms et al., 2017; Sternberg et al., 2018) as well as adverse effects.

On the other hand, EGFR targeting PKIs such as erlotinib, gefitinib or osimertinib have a limited action on the kinome and are more specific than antiangiogenic PKIs. Multiple studies failed to prove a relationship between exposure and efficacy (Brown et al., 2017; Hirose et al., 2016; Kobayashi et al., 2015; Xin et al., 2015), but a linear relationship between exposure and adverse effects remains. Therefore, the first category of PKIs is a better candidate for TDM.

4.2. Interests of therapeutic drug monitoring

Drug monitoring allows correcting the systemic exposure of a patient. Rousselot et al. randomised patients treated with imatinib for chronic myeloid leukaemia when the trough plasma concentration was too low, between a dose-increase strategy aiming to reach the threshold of 1000 ng/ml versus classic clinical imatinib management. Two-thirds of the patients were underexposed, and the rate of major molecular response was higher at one year with TDM (63% vs. 37%, p = 0031). For sunitinib, patients AUC is predictive of time to tumour progression and overall survival (Houk et al., 2010) and one-third of the patients seem to have a too low dosage (Lankheet et al., 2014). Sunitinib, sorafenib or everolimus among other PKIs (Gao et al., 2012) are good

Table 3
Phenomenon involved in PKI's pharmacokinetics and recommendations for clinical practice.

ADME	Pitfall	Potential consequences	Clinical recommendations
Absorption	Gastric surgery	Increase of gastric pH decreases PKI's bioavailability	Chose PKI with no influence of gastric acidity whenever possible. TDM can help when no alternatives are possible
	Proton pump inhibitors and anti-acids	Increase of gastric pH decreases PKI's bioavailability	PPI should be avoid whenever possible, anti-H2 should always be taken 2 hours after the PKI, direct anti-acid should be taken 2 hours after the PKI
	Food	Meals alter the gastric emptying and increase gastric pH, increasing or decreasing PKI's exposure.	Respect the fed or fasted recommendation for the drug
	Time of the day	Enzymes and transporters involved in the pharmacokinetics of PKIs have time-dependent variations in expression	Limited evidence of influence on the efficiency / toxicity
	Adherence	PKI's oral drug prescription is particularly at risk of non-adherence	Consider using adherence scales. TDM could be used in case of doubts
	Other sources of variation	Use of parasympatholytics or mimetics can change PKI's absorption	No evidence of influence on the efficiency or toxicity
Distribution	Protein Binding	Modification of the half-life	No evidence of influence on the efficiency or toxicity
	Sarcopenia	The combination of sarcopenia and BMI < 25 is a good predictor of PKI's toxicity	Sarcopenic patients should have a closer clinical monitoring. Consider beginning at lower dose.
	Obesity	Reduced absorption of oral drugs across the gut wall because of visceral fat, modified volume of distribution, increased drug metabolism, decreased clearance	Consider TDM when no adverse effects are seen
	Blood-brain barrier	Ability to cross the blood-brain barrier modify the efficiency of PKI on brain metastases and is critical for leptomeningeal diseases	PKI's BBB diffusion should always be considered for the treatment of any cancer with a brain lesion
Metabolism / Elimination	Cytochromes mediated drug-drug interaction	Most PKIs are at least partially metabolised through CYP3A4	Any drug that alters the CYP3A4 function should be suspected of drug interaction when a concomitant treatment with a PKI is started
	UGT	Inhibitory effects of PKIs on UDP-glucuronosyltransferase (UGT) activities	No evidence of influence on the efficiency or toxicity
	ABC transporters	Some PKIs are ABC transporters substrates and inhibitors	Avoid concomitant use of p-gp inhibitors with afatinib
	Genetic polymorphism	Patients can be poor metabolizers, intermediate metabolizers, extensive metabolizers, or ultra-extensive metabolizers	Not indicated in daily care
	Tobacco	Induction of CYP1A2	Whenever possible, consider using alternatives to erlotinib with smokers ($>$ 10cig/day). Consider increasing the dosage if erlotinib is maintained
	Renal failure	Patients at risk of cardio-vascular complications for anti-angiogenics. No significant or mild pharmacokinetic modifications for most PKIs	Consider beginning at lower dose. For PKIs with no data, consider TDM. For anti-angiogenics, monitor closely cardio-vascular complications
	Hepatic failure	Decreased clearance	For Child-pugh A patients: normal dose and closer clinical monitoring. For more important hepatic failure, begin at lower dose and consider TDM, when the drug is not clearly contre-indicated

candidates for TDM although no randomised trial has proven better clinical outcome with TDM yet. The intra-patient variability could also make it challenging. In a small cohort (13 patients), de Wit et al. (de Wit et al., 2015) evaluated if a PK-guided strategy could increase the percentage of patients within the target window of AUC. The study was terminated early due to high intra-patient plasma concentration variations.

Although the usefulness of generalised PK-guided dosing strategies remains to be proven in randomised trials, TDM could help with the management of patients with predictive factors of pharmacological failure. We summarised in Table 3 situations where TDM could be useful.

5. Conclusion

With the approval of more and more of these molecules in oncology, it is difficult to know everything about the pharmacology of PKIs. However, basic knowledge of the pharmacology of PKIs is needed for the safe use of this class of drugs. We reviewed and synthesized relevant information in order for clinicians to avoid major pitfalls.

The bioavailability of a PKI could be compromised when gastric acidity is modified by either gastrectomy, proton pump inhibitors or food. Adherence is an important cause of treatment failure and should be explored when no toxicity is seen for a patient. Sarcopenia is an independent marker of toxicity and the tolerance to PKIs of sarcopenic patients should be closely monitored. Most PKIs are metabolised by CYP3A4. Drug-drug interaction and herb-drug interaction through CYP3A4 should be anticipated and concomitant CYP3A4 modifiers prescription changed whenever possible. Hepatic failure could compromise PKI treatment. Renal failure and haemodialysis have no major effect on PKIs but could be associated with an increase of cardio-vascular events for patients treated with PKIs, in this fragile population.

Whenever there is a predictive risk of underdosing a patient, for obese patients for example, therapeutic drug monitoring can help to reach a target window of AUC.

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