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THERAPIES

HEADING: Hemato-oncopharmacology

Pharmacokinetics and therapeutic drug monitoring of anticancer protein/kinase inhibitors

PK and TDM of anticancer PKIs

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Summary

Over the past two decades, protein/kinase inhibitors, as targeted therapies, raised in number and have become increasingly mainstream in the treatment of malignant diseases, thanks to the ease of oral administration and the minimal adverse drug reactions. These drugs have similar pharmacokinetic properties: a relatively good absorption and distribution, a strong hepatic metabolism, and a mainly biliary excretion. However, this pharmacokinetic and route of administration has the disadvantage of resulting in a large inter- and intra-individual variability. Despite this significant variability, these drugs are largely prescribed at the same initial dose for quite all patients (flat dose), even though this variability would require individualized adaptation for each patient and/or each new circumstance. Promptly after their commercialization, scientific teams have performed concentration measurements of several drugs and showed the existence of efficacy or toxicity thresholds. This has contributed to the development of therapeutic drug monitoring as one of the strategies to improve the response and reduce the adverse reactions of these drugs. There is still a need to determine precise thresholds for the remaining drugs and to evaluate the impact of TDM in therapeutic management. In order to determine the current state of the art, this article reviews indications, pharmacokinetics and TDM data for 49 marketed PKIs.

KEYWORDS

Therapeutic drug monitoring; Protein/kinase inhibitors; Cancer drugs

Abbreviations

ADR: adverse drug reaction

AGP: alphasialoprotein acid

AML: acute myeloblastic leukemia

ATP: adenine tri-phosphate

AUC: area under curve

CLL: chronic lymphocytic leukemia

C_{max} : maximal concentration

C^{min} : minimal (trough) concentration

CML: chronic myeloid leukemia

CV: coefficient of variation
CYP: cytochrome P450
DBS: dried blood spot
GIST: gastrointestinal stromal tumour
HES: hypereosinophilic syndrome
HPLC: high-performance liquid chromatography
MA: marketing authorisation
MDS: myelodysplastic syndrome
MPS: myelo-proliferative syndrome
NSCLC: non-small cell lung cancer
PKI: protein/kinase inhibitor
RCC: renal cell carcinoma
TDM: therapeutic drug monitoring
TKI: tyrosine kinase inhibitor
 T_{\max} : time at C_{\max}
UGT: uridine 5'-diphospho-glucuronosyltransferase

Introduction

Advances in chemotherapy have accelerated in recent decades. Changes in the rate of administration of these drugs have made it possible to better match the drug to the rapid renewal of tumour cells. However, adverse drug reactions (ADRs) often limit the use of conventional chemotherapy in sufficient doses. The use of therapeutic drug monitoring (TDM) has improved the management and dosage of drugs to reduce these ADRs, but they remain significant, as they are mostly due to a lack of specificity against tumour cells. The understanding of the mechanisms linked to tumour growth has allowed the development, since the early 2000s, of molecules targeting not only the tumour cell, but more particularly the protein or proteins involved in their growth. Among these so-called targeted therapies, inhibitors, initially of tyrosine kinases inhibitors (TKI) and now of other proteins/kinases inhibitor (PKI), are now widely used in the treatment of various malignant diseases. These low molecular weight drugs can bind competitively to the adenine tri-phosphate (ATP) binding site of the catalytic domain of tyrosine kinases, whether they are transmembrane (most often acting as a receptor) or intracytoplasmic. In the case of proteins other than tyrosine kinases, the drug can bind directly to the protein and inhibit its main function (example of PARP proteins). Currently, more than 40 protein/kinase inhibitors (PKIs) are marketed and more than 50 are being tested in different phases of clinical trials. These PKIs represent a major advance in the treatment of malignant diseases such as chronic myeloid leukaemia (CML), gastrointestinal stromal tumour (GIST) or other solid tumours, the range of cancers treated of which is constantly expanding. However, the efficacy of these drugs is not always optimised, which can compromise the response to these drugs, despite the hopes raised during clinical trials. Indeed, some patients are non-responders, due to pharmacokinetic, pharmacodynamic or pharmacogenetic characteristics, and it is becoming necessary to implement strategies that take these characteristics into account in order to improve the response to these drugs. Among these strategies, one of the easiest and most accessible is TDM.

Indications for PKIs

PKIs are part of the so-called “targeted” therapies, and are therefore able to bind at least one protein or tyrosine kinase. Inhibition of this protein often determines the indication because these diseases involve mutations in one or two specific proteins. In the cancers targeted by the PKIs, we can distinguish haematological pathologies with “liquid” tumours and carcinomas localised in certain organs with solid tumours.

“Liquid” tumours

Imatinib (Glivec[®], Gleevec[®]) was the first tyrosine kinase inhibitor developed to target Bcr-Abl and was marketed in 2001. It has become the gold standard of treatment in first-line CML due to its efficacy and good safety. Its successors in this disease are dasatinib (Sprycel[®]) and nilotinib (Tasigna[®]), which were more recently introduced to the market first as second-line and then as first-line treatments. The two other drugs marketed in this indication were bosutinib (Bosulif[®]) and ponatinib (Iclusig[®]), the latter targeting the lethal T315 mutation of Bcr-Abl.

Imatinib and dasatinib have also received marketing authorisation (MA) for refractory Philadelphia chromosome-positive acute lymphoblastic leukaemia (Ph + ALL). Only imatinib has additional indications such as myelodysplastic/myeloproliferative syndromes (MDS/MPS) and hypereosinophilic syndromes (HES) associated with platelet-derived growth factor receptor (PDGFR) and FIP1L1-PDG gene rearrangements, respectively.

Other hematological diseases can now be targeted with PKIs: first, acute myeloblastic leukemia (AML), which often has mutations on FLT3 or BCL-2, can be treated with gilteritinib (Xospata[®]) and midostaurin (Rydapt[®]). For chronic lymphocytic leukemia (CLL), there are several subpopulations of patients with different mutations who can be treated with Bruton kinase inhibitors such as ibrutinib (Imbruvica[®]) and acalabrutinib (Calquence[®]), an IP3K inhibitor, idelalisib (Zydelig[®]), or a BCL-2 inhibitor, venetoclax (Venclyxto[®]).

Solid tumours

Other tyrosine kinases, PDGFR and c-Kit, are often found mutated, and thus activated, in GIST. Because of their inhibition of c-Kit and/or PDGFR, imatinib, sunitinib (Sutent[®]), regorafenib (Stivarga[®]) and avapritinib (Ayvakit[®]) are used in this indication, alone or in

combination. Its action on PDGFR also indicates imatinib in dermatofibrosarcoma protuberans.

PKIs are used to limit cell proliferation in other diseases. For example, lapatinib (Tyverb[®]) reversibly inhibits the HER1 (= ErbB1 or EGFR) and HER2 (= ErbB2) tyrosine kinases involved in the growth and survival of various solid tumours, such as metastatic breast cancer, where it is used in combination. Tucatinib (Tukysa[®]), a potent and selective HER2 inhibitor, is also marketed in this indication. It is of note that some breast cancers involve other signalling pathways such as CDK, PARP or PI3K: abemaciclib (Verzenio[®]), Palbociclib (Ibrance[®]), Ribociclib (Kisqali[®]) (CDK4/6 inhibitors), Olaparib (Lynparza[®]), Rucaparib (Rubraca[®]), Talazoparib (Talzenna[®]) [PARP inhibitors] or alpelisib (Piqray[®]) [PI3K inhibitor] also have this indication.

Compared to lapatinib, erlotinib (Tarceva[®]) and gefitinib (Iressa[®]) more specifically inhibit EGFR and are indicated in locally advanced or metastatic EGFR-mutated non-small cell lung cancer (NSCLC).

PKIs such as sorafenib (Nexavar[®]), sunitinib and pazopanib (Votrient[®]), which have an anti-angiogenic action via their action on VEGF receptors, are indicated in renal adenocarcinoma, but also in liver (sorafenib) or pancreatic (sunitinib) cancers. Pazopanib can also be used in soft tissue sarcomas, as is the TRK inhibitor larotrectinib (Vitrakvi[®]).

Basal cell carcinomas involves mutations in the hedgehog pathway, with an important role the SMO protein that can be inhibited by sonidegib (Odomzo[®]) and vismodegib (Erivedge[®]).

Similarly, the MAPK pathway and in particular the RAF and MEK kinases often have mutations involved in some melanomas. RAF inhibitors such as vemurafenib (Zelboraf[®]), encorafenib (Braftovi[®]) and dabrafenib (Tafinlar[®]) will be used in combination with the MEK inhibitors cobimetinib (Cotellic[®]), binimetinib (Mektovi[®]) and trametinib (Mekinist[®]), respectively, to treat these cancers.

Another MEK inhibitor, selumetinib (Koselugo[®]), can be used alone in neurofibromatosis.

Simplified general mechanism of action of PKIs

In a first step, protein/kinase inhibitors have to cross the plasma membrane, either passively or by using transporters, in order to bind instead of ATP to the intracellular domain of RTKs or intracellular proteins. By occupying this site, PKIs prevent the autophosphorylation and dimerization of protein-kinases or inhibit directly the protein, thus blocking signal transduction (Fig. 1).

Pharmacokinetics of PKIs

Generally, pharmacokinetics can be defined as the measurement and interpretation of the time course of drug concentrations in any of the different regions of the body in relation to dosage: "what the body does to the drug". In practice, pharmacokinetics focuses mainly on drug concentrations in blood plasma, which is the easiest compartment to access for biological sampling.

The evolution of concentrations of therapeutic substances in blood is guided by four different phases: absorption, distribution, metabolism and elimination for which different parameters are associated. Table 2 shows the main pharmacokinetic characteristics of protein/kinase inhibitors.

Absorption of PKIs

Marketed PKIs show large differences in the extent and timing of absorption after oral administration.

Acalabrutinib, larotrectinib, dasatinib or selumetinib could be absorbed very quickly under normal conditions; among others, imatinib, nilotinib, dabrafenib and pazopanib are rapidly absorbed from the gastrointestinal tract, with peak absorption occurring between 2 and 4 hours. Erbb (EGFR, HER2) inhibitors have a mean time to absorption of about 4 hours, with gefitinib being more variable at 3-7 hours. Sunitinib, palbociclib or vandetanib are absorbed more slowly with a T_{max} of between 5 and 12 hours. Finally, vismodegib has a very variable peak absorption, as it can be absorbed as early as 1 h, but also very late, up to nearly 7 days.

Bioavailability (amount of drug reaching the systemic circulation compared to the intravenous route) is very different between drugs ranging from 14% (pazopanib) to almost 100% (imatinib). It is of note that ibrutinib has a very low rate of absorption (<3%) that could lead to large variability between patients. At least, half of drugs have not had their bioavailability studied in humans, but the values of several could have been extrapolated (e.g. lapatinib, or sunitinib and dasatinib).

The pharmacokinetics of PKIs may not be affected by food intake (e.g. imatinib, dasatinib, gefitinib, sunitinib...) and, in this case, could be administered with or without meals. However, imatinib is best administered with meals because of better digestive tolerance. In the presence of a high-fat diet, the bioavailability of PKIs, when it varies, most often increases, while that of sorafenib, gilteritinib, dabrafenib or trametinib decreases. It is therefore recommended that these drugs be taken at least 1 h before or 2 h after a meal in order to achieve uniform exposure during treatment or to avoid excessive concentrations at peak plasma levels.

Distribution of PKIs

PKIs are generally very well distributed in tissues, including cancer tissues, with volumes of distribution ranging globally from 150 to over 2500 L. Only few drugs present a volume of distribution lower than that of a human body (acalabrutinib, pazopanib, larotrectinib, vismodegib and dabrafenib).

Most of the drugs described in the table are more than 90% bound to plasma proteins (mainly albumin and alpha₂-glycoprotein), with very high binding reported for, example, axitinib, cabozantinib, pazopanib, ponatinib, regorafenib, sorafenib, venetoclax or lapatinib (>99%). It is therefore possible that in cases where the amount of alpha₂-glycoprotein is increased, or during inflammation [1], exposure to PKIs may be altered; for example, alpha₂-glycoprotein acid (AGP) has been found to be a cofactor for imatinib exposure [2]. Only ten or so PKIs are fixed at less than 90% (Table 2) and are therefore little affected by a variation in the quantity of plasma proteins, notably alpelisib, fixed at only 11%.

Metabolism of PKIs

Another common feature of these drugs is that they are all metabolised primarily by CYP3A4 and to a lesser extent by other CYPs or uridine 5'-diphospho-glucuronyltransferases (UGTs), with the exception of talazoparib and afatinib that are not metabolised, or alpelisib, idelalisib and trametinib that are metabolised by oxydases. Other enzymes may be involved, but to a lesser degree. With the exception of nilotinib, dabrafenib, alectinib, acalabrutinib, midostaurin and regorafenib, the metabolised drugs yield an active metabolite(s) that is only about or less than 20% of the amount of the parent drug.

Elimination of PKIs

Excretion of the majority of these compounds and their metabolites is predominantly biliary and only a small fraction of these compounds are eliminated via the urine (<35% in urine), excepted for talazoparib, more than 55% excreted through the urinary tract. The half-lives (T_{1/2}) are highly variable: from 3 to 6 hours for dasatinib to more than 28 days for sonidegib.

With the exception of 6 drugs, whose T_{1/2} are higher (Table 2), the PKIs have a T_{1/2} of less than 60h, allowing steady-state concentrations to be achieved in less than 2 weeks.

Variability of response to PKIs

PKIs have shown efficacy in vitro in malignant cell lines overexpressing target protein/kinases. In clinical trials, they have often shown superior efficacy to existing drugs, particularly in terms of overall survival or progression-free survival, combined with a reduction in overall toxicity. However, despite their very good efficacy, residual disease persists in some patients and some will progress or become resistant to treatment, either initially or at a later stage.

Concept of poor responders

The notion of response is based on recommendations using markers, pathophysiological characteristics, biological or medical imaging data. The notion of non-response, poor response

or even progression can be based on these same criteria. However, the levels of recommendations and the resulting therapeutic decision are not the same for all diseases. For example, in the treatment of CML with imatinib, the European LeukemiaNet group has proposed relatively precise recommendations concerning response and non-response [3].

These recommendations are different when the treatment concerns second-generation PKIs in second-line or now first-line treatment.

For solid tumours, and in particular GIST, the guidelines are mainly based on the occurrence of an event, such as progression, rather than response [4, 5]. Risk assessment strategies based on mitotic counts, tumour size, and tumour location help in the choice of routine follow-up. High-risk GIST patients usually progress after 2-3 years, but this is much later for low-risk patients. The impact on treatment strategy will therefore not be the same in these conditions, nor will the consequences of variability.

Sources of variability

A variety of factors may be at the root of these inefficiency problems:

- Biological/pharmacodynamic factors such as the initial presence or emergence of mutations in the genes coding for the target protein tyrosine kinases, the development of secondary signalling pathways, etc;
- Clinical factors with a poor prognosis at the time of management (such as large tumour mass, metastases, etc.);
- Factors affecting pharmacokinetics.

Pharmacokinetic variability

PKIs have a pharmacokinetic profile that can be described as favourable, as most have rapid absorption and good bioavailability. However, all these drugs have pharmacokinetic characteristics that may vary over time and between individuals: PKIs are generally administered orally and CYP3A4 is mainly responsible for their metabolism. In the various published series on PKIs (except phase I or studies of less than 50 subjects), we have not been

able to identify inter-individual variations of less than 40%. The reasons for these variations in plasma concentration are not fully understood, but may probably include

- Less than complete adherence to dosages;
- Demographic variation factors, such as gender, age, weight, body surface area, etc;
- Differences in absorption in the gastrointestinal tract;
- Intrinsic variability in the activity of metabolic enzymes (CYP3A4) or drug interactions on these enzymes;
- Differences in protein binding (albumin, alpha-glycoprotein);
- Differences in cellular penetration and efflux of the drugs.

All these pharmacokinetic variations are summarised on Fig. 2 [6].

Impact of variability

As previously shown, the sources of variability are profuse and of very diverse origins: demographic characteristics (age, sex, ethnicity), clinical-biological (hypoalbuminemia, inflammation, liver failure, etc.), genetic (polymorphisms of enzymes responsible for drug metabolism, efflux proteins and action targets), pharmacokinetic interactions (drugs, complementary medicines) and drug compliance.

This results in very high coefficients of variation (CV): Widmer et al. [7] reported CVs varying from 9 to 221% among some PKIs. Despite the fact that CYP450 explains a large part of this CV, drugs such as afatinib have been described with a CV of 221% while it is not metabolized (or very little) by CYPs. This large CV is involved in the risk of a lack of efficiency or risk of toxicity.

Despite this significant variability, these drugs are widely prescribed at the same initial dose for all patients (flat dose), with the exception sometimes of patients with renal or hepatic impairment, for whom adaptations could be recommended.

The recommended dose is indicative and based on the results of the pivotal trial. In view of the above arguments, this dose is not necessarily optimal in patients with several co-morbidities and numerous associated drugs, hence the need for individualized adjustment for each patient and/or each new treatment circumstance.

Therapeutic drug monitoring

Although the pharmacokinetic profile of PKIs is theoretically very good in the context of oral chemotherapy, the existence of very significant pharmacokinetic variability suggests the interest of individualised dose adjustment according to concentration. TDM can help to reduce the variability due to pharmacokinetics. The goals of TDM are to reduce the rate of therapeutic failures due to poor compliance or insufficient dose, and to reduce the frequency of adverse and/or toxic drug reactions due to excessive concentration.

Mueller-Schoell *et al.* [8] compiled these concentration-efficacy and concentration-toxicity data and determined a recommendation level for TDM (in the Table 3, they are shown between I for those with a highly recommended TDM and IV for those with no interest for TDM at all). The older drugs having more data, they often have a higher grade (I or II in the table) or, on the contrary, have failed to demonstrate an interest (grade IV).

The most recent ones are still only at an exploratory level (III) but have many similarities with the older ones, which makes them drugs with a great potential for TDM.

The TDM of these drugs is quite simple to set up: just wait until the drug is at the steady-state concentration, which only takes a fortnight at the most (Table 3) and take the sample on the right tube (most often lithium heparin or EDTA), at the right time (most often in residual), which is probably the most constraining part.

The analysis is most often performed in high-performance liquid chromatography (HPLC) coupled with mass spectrometry or at least ultra-violet detection (immunoassay analyses have been developed but few are available). There are increasingly more methods to measure several PKIs at the same time [9-13].

These analyses are covered and fully reimbursed by the French social security system for an amount of just under €40. This allows all patients and doctors to have access to TDM. This care is now improved by the existence of more and more research on dried blood spot (DBS) (e.g. imatinib analysis [14-16]) or microsampling systems: the patient pricks his finger at the right time, deposits a drop of blood on a card/system and send it by regular mail.

As shown in Table 3 [17-57], there are still only a few drugs for which real thresholds exist. It is therefore still very important to define efficacy and toxicity thresholds, either through adapted studies or by using existing data from pivotal studies. The next step to increase the level of TDM recommendation for these drugs is to show that adaptation on the basis of these thresholds can modify the clinical outcome

Currently, only dasatinib has had a concentration-controlled trial that has formally demonstrated the benefit of using TDM to individualise dosing, with reduction in ADRs without loss of efficacy.

Conclusion

The arrival of PKIs in the management of cancers has dramatically changed the management of these malignant diseases, in particular thanks to the chronic oral intake and the reduction of ADRs, making these drugs less burdensome for patients than conventional chemotherapy. While PKIs have long been confined to a "one size fits all" strategy, various studies have begun to show the value of individualised doses, relying heavily on TDM. However, there is still a lot of work to be done to define efficacy and toxicity thresholds and to show that their application can still evolve towards a better use of these drugs.

Disclosure of interest

SB: occasional interventions: consulting activities for Pierre Fabre; Conferences: invitations as speaker for Novartis, BMS, Boehringer and Incyte, Study collaboration with Boehringer.

MM: Conferences: invitations as speaker for Novartis and Incyte, study collaboration with Boehringer.

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Table 1. Indications of PKIs: ● Indications from the Epars of each molecule ○ Phase III studies (from clinicaltrials.org)

Table 2. Pharmacokinetics data of PKIs (from the Epars of each drug)

Drugs	Primary therapeutic target	Absorption		Distribution		Metabolism	Excretion	Elimination
		F	Tmax	Vd (L)	Prot binding			
Acalabrutinib CALQUENCE®	BTK (Bruton)	25% □	0.5-1.5h	34	~ 98%	Mainly hepatic through CYP3A and GST	Mainly biliary (>84 %)	1-2h 7h (Active M)
Ibrutinib IMBRUVICA®	BTK (Bruton)	2.9% □□	1-2h	10 000	97%	Mainly hepatic through CYP3A4	80 % Biliary 10 % Urinary	4 – 13 h
Alpelisib PIQRAY®	PI3Ka	69% □□	2-4h	114	11%	Chemical and enzymatic hydrolysis of amides	81 % Biliary 13 % Urinary	9 h
Idelalisib ZYDELIG®	PI3K	ND	2-4h	96	~ 94%	aldehyde oxydase	78 % Biliary 15 % Urinary	8 h
Gilteritinib XOSPATA®	FLT3, AXL	ND □□	4-6h	1100	~90%	Hepatic through CYP3A4	65 % Biliary 16 % Urinary	113 h
Midostaurin RYDAPT®	FLT3, Kit, PDGFR, VEGFR, PKC...	ND	1-3h	95	~ 98%	Hepatic through CYP3A4 1 active metabolite (~28 % AUC midostaurin)	Mainly biliary (~78 %)	21 h
Venetoclax VENCLYXTO®	BCL-2	ND □□	5-8h	256-321	>99%	Mainly hepatic through CYP3A4	Biliary only	26 h
Bosutinib BOSULIF®	Bcr-Abl, Src, Lyn, Hck	ND □□	6h	10 000	~96%	Mainly hepatic through CYP3A4	Mainly biliary (~92 %)	34h
Dasatinib SPRYCEL®	Bcr-Abl, Src-kinases PDGFR ... + de 30 PK	~80 %	0.5-3h	2500	~ 96%	Mainly hepatic through CYP3A4	85 % Biliary 4 % Urinary	3 – 6 h
Imatinib GLIVEC®/GLEEVEC®	Bcr-Abl, Filp1 PDGFR, Kit	~98 %	2-4h	295-590	~ 95%	Mainly hepatic through CYP3A4/5; 1 active metabolite (~16 % AUC imatinib)	68 % Biliary 13 % Urinary	18 – 22 h
Nilotinib TASIGNA®	Bcr-Abl PDGFR, Kit	~ 30 % □□	2-4h	579-800	~ 98%	Mainly hepatic through CYP3A4	Biliary only	17 h

Ponatinib ICLUSIG®	Bcr-Abl (+Bcr-AblT315I) Kit, FLT3, RET, PDGFR, VEGFR	ND	4h	1100	>99%	Mainly hepatic through CYP3A4	87 % Biliary 5 % Urinary	22 h
Avapritinib	PDGFR, Kit	ND	2-4h	17L/kg	~ 98%	Mainly hepatic through CYP3A4/5 and CYP2C9	70 % Biliary 18 % Urinary	32-57 h
AYVAKYT®		□□						
Pazopanib VOTRIENT®	VEGFR PDGFR, Kit	14-39% □□	2-4h	~9-13	~ 99%	Mainly hepatic through CYP3A4	Mainly biliary (~90 %)	30 h
Sunitinib SUTENT®	VEGFR PDGFR, Kit, Flt3	ND	6-12h	2230	~95%	Mainly hepatic through CYP3A4. 1 active metabolite (~20 % AUC sunitinib)	61 % Biliary 16 % Urinary	40 – 60 h
Axitinib INLYTA®	VEGFR	58,0%	4h	160	>99%	Mainly hepatic through CYP3A4	60 % Biliary 23 % Urinary	2.5 – 6 h
Cabozantinib CABOMETYX®	VEGFR, MET, RET	ND □□	3-4h	319	>99%	Mainly hepatic through CYP3A4 4 active metabolites (>10% AUC cabozantinib)	54 % Biliary 27 % Urinary	99 h
Lenvatinib LENVIMA®	VEGFR, FGFR, RET, PDGFR, Kit	70-85%	1-4h	43-121	~98.5%	Mainly hepatic through CYP3A4	66 % Biliary 25 % Urinary	28 h
Regorafenib STIVARGA®	VEGFR Kit, RET, RAF-kinases, ...	<70% □□	4h	76	~99.5%	Hepatic through CYP3A4 and UGT1A9. 2 active metabolites (>50% AUC regorafenib)	71 % Biliary 19 % Urinary	20 – 30 h 60 h for M-5
Sorafenib NEXAVAR®	VEGFR, PDGFR, Kit, Flt3 RAF-kinases, ...	38-49% □□	2-6h	213-400	~99.5%	Hepatic through CYP3A4 and UGT1A9. 1 active metabolite	77 % Biliary 19 % Urinary	25 – 48 h
Vandetanib CAPRELSA®	VEGFR, EGFR, RET	ND	4-10h	7500	~94%	Mainly hepatic through CYP3A4	60 % Biliary 30 % Urinary	19 d
Larotrectinib VITRAKVI®	TRK	34% □⇒	1h	48	~70%	Mainly hepatic through CYP3A4/5	58 % Biliary 39 % Urinary	3 h
Sonidegib ODOMZO®	SMO (Hedgehog pathway)	ND □□	2-4h	9170	> 97%	Mainly hepatic through CYP3A4	Mainly biliary (>93 %)	28 d
Vismodegib ERIVEDGE®	SMO (Hedgehog pathway)	32% □⇒	1h-7d	16-24	> 97%	Low metabolism CYP2C9	Mainly biliary (>82 %)	12 d
Alectinib	ALK, RET	37%	4-6h	475	>99%	Mainly hepatic through CYP3A4	Mainly biliary	32 h

ALECENSA®		□□					1 active metabolite (~40% AUC alectinib)	(>98 %)	30 h pour M-4
Brigatinib	ALK, ROS1	ND	1-4h	307	~91%		Mainly hepatic through CYP2C8 and CYP3A4 (minority)	65 % Biliary	24 h
ALUNBRIG®		□⇒						25 % Urinary	
Ceritinib	ALK	~ 25 %	4-6h	ND	~97%		Mainly hepatic through CYP3A	68 % Biliary	31 – 41 h
ZYKADIA®		□□						2 % Urinary	
Crizotinib	ALK	43%	4-6h	1700	~ 91%		Mainly hepatic through CYP3A4	63 % Biliary	42 h
XALKORI®								22 % Urinary	
Lorlatinib	ALK, ROS1	81%	1-2h	121	66%		Mainly hepatic through CYP3A4 and UGT1A4	48 % Biliary	24 h
LORVIQUA®		□⇒						41 % Urinary	
Afatinib	EGFR = HER1	ND	2-5h	4500	~95%	∅		Mainly biliary (>85 %)	37 h
GIOTRIF®									
Erlotinib	EGFR = HER1	~ 59 %	4h	232	~95%		Hepatic through CYP3A4 and CYP1A2	Mainly biliary (>90 %)	36 h
TARCEVA®		□□					2 active metabolites (~10 % AUC erlotinib)		
Gefitinib	EGFR = HER1	~ 59 %	3-7h	1400	~90%		Mainly hepatic through CYP3A4/5 and CYP2D6	Mainly biliary (>90 %)	42 h
IRESSA®									
Osimertinib	EGFR T790M	ND	6h	986	High		Mainly hepatic through CYP3A4/5	68 % Biliary	48 h
TAGRISO®		□						14 % Urinary	
Lapatinib	ErbB2 = HER2	ND	4h	2200	>99%		Mainly hepatic through CYP3A4/5 and CYP2C19, 2C8	Mainly biliary (>90 %)	24 h
TYVERB®									
Tucatinib	ErbB2 = HER2	ND	2h	1670	~97%		Mainly hepatic through CYP2C8 and CYP3A4 (minority)	Mainly biliary (>86 %)	9 h
TUKYSA®		□⇒	(1-4h)						
Abemaciclib	CDK4/6	45%	8h	750	~ 97%		Hepatic through CYP3A4	Mainly biliary (>81 %)	25 h
VERZENIOS®		□⇒							
Palbociclib	CDK4/6	46%	6-12h	ND	85%		Mainly hepatic through CYP3A and SULT2A1	74 % Biliary	28 h
IBRANCE®		□						17 % Urinary	
Ribociclib	CDK4/6	ND	1-4h	1090	~70%		Mainly hepatic through CYP3A4	69 % Biliary	32 h
KISQALI®		□⇒						22 % Urinary	
Olaparib	PARP		1-3h	167	~82%		Mainly hepatic through CYP3A4	44 % Biliary	12 h

LYNPARZA®		□□						42 % Urinary	
Rucaparib	PARP	ND	2h	113-262	~70%	Mainly hepatic through CYP2D5 and minority CYP1A2 and CYP3A4		72 % Biliary	26 h
RUBRACA®								17 % Urinary	
Talazoparib	PARP	ND	1-2h	420	~74%	⊗		Mainly urinary (>55 %)	90 h
TALZENNA®		□⇒							
Dabrafenib	BRAF (+BRAFFV600)	95%	2h	46	~99.7%	Hepatic through CYP3A4 and CYP2C8. 2 active metabolites (>50 % AUC Dabra)		71 % Biliary	8 – 10 h
TAFINLAR®		□□						23 % Urinary	
Encorafenib	BRAF (+BRAFFV600)	<86%	1.5-2h	226	~86%	Mainly hepatic through CYP3A4		47 % Biliary	6 h
BRAFTOVI®		□						47 % Urinary	
Vemurafenib	BRAF (+BRAFFV600)	ND	4h	90	>99%	Mainly hepatic through CYP3A4		Mainly biliary (>90 %)	50 h
ZELBORAF®		□□							
Binimetinib	MEK	<50%	1.5h	374	~ 97%	Mainly UGT		62 % Biliary	9 h
MEKTOVI®		□⇒						31 % Urinary	
Cobimetinib	MEK	46%	2.4h	800	~ 95%	Hepatic through CYP3A4 and UGT2B7		Mainly biliary (>90 %)	44 h
COTELLIC®									
Selumetinib	MEK	62%	1h	146	~90%	Hepatic through CYP3A4/5 and minority CYP2C19, CYP1A2 and UGT1A		59 % Biliary	~ 14 h
KOSELUGO®		□						33 % Urinary	
Trametinib	MEK	72%	1.5h	1200	~ 97%	Carboxylesterases		80 % Biliary	5.3 d
MEKINIST®		□□						19 % Urinary	
Pemigatinib	FGFR	ND	1-2h	235	~91%	Mainly hepatic through CYP3A4		Mainly biliary (>82 %)	15h
PEMAZYRE®		□⇒							

Table 3. Recommended/observed value and steady state of PKI

Drug	Steady State (days)	Disease/ organ	Recommended or [Observed value] (ng/mL)	Recommendation level	References other than EPARs
Abemaciclib	5	Breast	[181]	III	[17]
Acalabrutinib	2	CLL	[AUC: 1208 (25%); C _{max} : 1120 (30%)]	IV	[18, 19]
Afatinib	8	NSCLC	T<34 [14.4-27.4]	II*	[20]
Alectinib	7	NSCLC	E≥435	II	[21]
Alpelisib	2	Breast	[AUC: 33224]	III	
Avapritinib	12	GIST	[593]	III	
Axitinib	3	RCC	E≥5	I	[22]
Binimetinib	2	Melanoma	[53.3]	II*	
Bosutinib	5	CML	E≥63; T<91 [112-147]	III	[23]
Brigatinib	5	NSCLC	[520]	III	
Cabozantinib	15	RCC, liver	[1125]	III	[24]
Ceritinib	8	NSCLC	[871]	III	
Cobimetinib	10	Melanoma	[127]	III	
Crizotinib	9	NSCLC	E≥235	II	[21, 25]
Dabrafenib	2	Melanoma	T<50	II*	[26]
Dasatinib	2	CML	T<1.5	I*	[27, 28]
Encorafenib	2	Melanoma	[23]	III	
Erlotinib	8	NSCLC	E≥500	II	[29]
Gefitinib	10	NSCLC	E≥200	I	[30]
Gilteritinib	24	AML	E≥100 [456]	III	
Ibrutinib	2	CLL	[AUC: 680]	III*	[31]
Idelalisib	2	CLL	[426]	III	
Imatinib	4	CML	E≥1000	I	[32-34]
		GIST	E≥1100 (at 1m), ≥800 (after 3m)	I	[35, 36]
Lapatinib	5	Breast	300-600 [490, 780]	III	[37, 38]
Larotrectinib	1	Soft tissue sarcoma	[5]	IV	
Lenvatinib	5	Liver	[43.4, 95.6]	III	[39]
Lorlatinib	5	NSCLC	[70-125]	III	
Midostaurin	28	AML	[919-1060 (54%)]	III	
Nilotinib	4	CML	E ≥ 600	II	[40]
Olaparib	3	breast	[1570, 1860]	III	[41]
Osimertinib	12	NSCLC	[166]	III	
Palbociclib	6	Breast	[61]	III	
Pazopanib	7	RCC & GIST	E≥20500	I	[42-44]
Pemigatinib	3	Cholangiocarcinoma	[C _{max} : 236 nM (CV 56%)]	III	
Ponatinib	5	CML	[34]	III	[45]
Regorafenib	5	GIST, liver	[1400]	III	
Ribociclib	7	Breast	[732]	III	

Rucaparib	6	Breast	[1754±805]	III	
Selumetinib	3	Neurofibromatosis	[C _{min} : 57 (44%), C _{max} : 731 (62%)]	III	
Sonidegib	140	Basal cell carcinoma	[830 (200 - 2400)]	III	
Sorafenib	8	RCC, liver	[3750]	III	[46]
Sunitinib	10	RCC, GIST	E≥50	I	[47]
Talazoparib	20	Breast	[3.5]	III	
Trametinib	15	Melanoma	E≥10.6	I	[48]
Tucatinib	4	Breast	[C _{max} : 790-1120, AUC: 3000-4080)	III	[49]
Vandetanib	95	Thyroide	[795]	III	
Vemurafenib	12	Melanoma	E≥42000	II	[50-52]
Venetoclax	6	CLL	[520]	III	[53]
Vismodegib	60	Basal cell carcinoma	[11367±4084]	IV	

AUC: area under curve; E: efficacy; T: toxicity,

AUCs are expressed in ng.h/mL

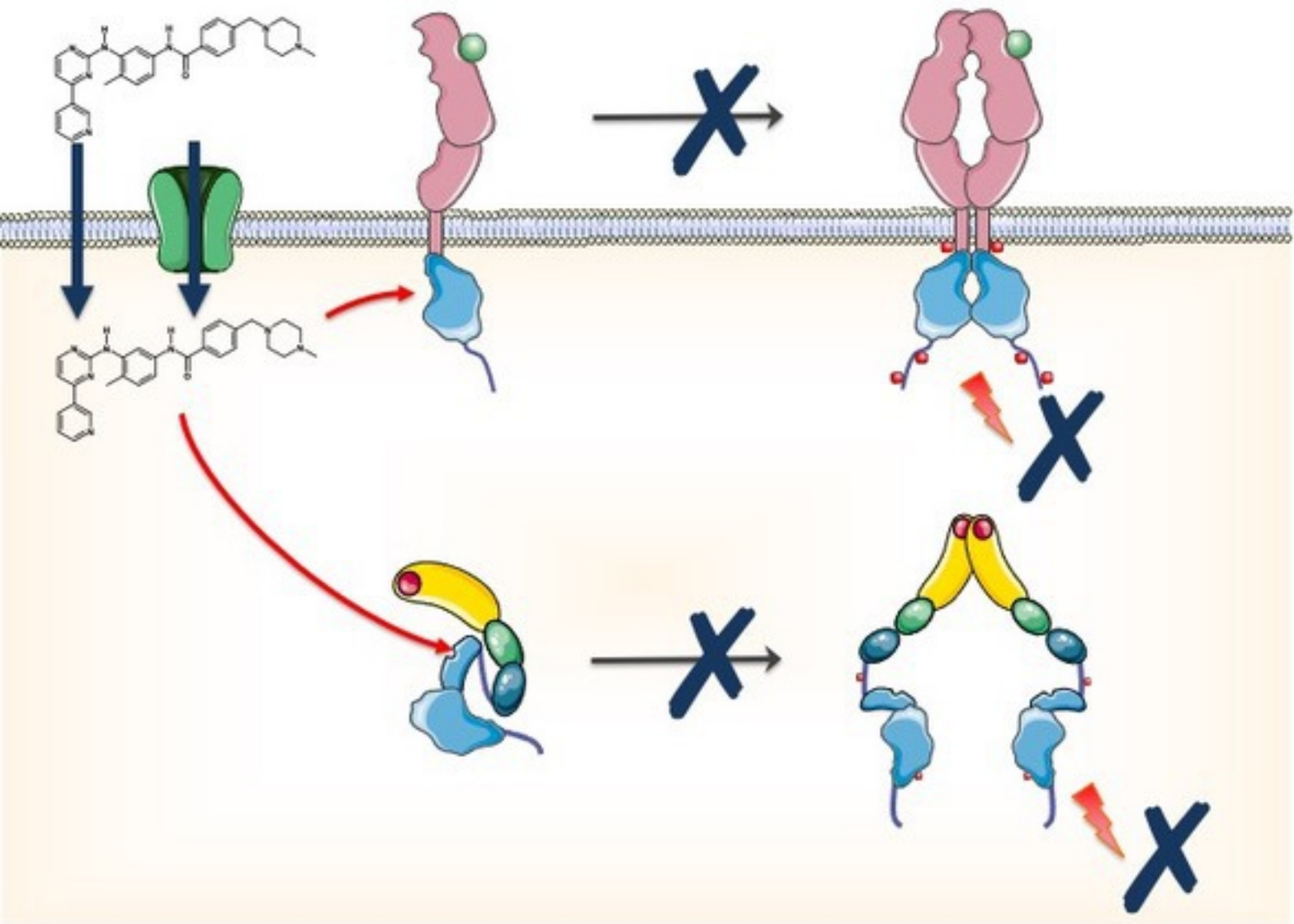
* points out a discrepancy with the cited article (contribution of new data).

Figure legends

Figure 1. Simplified mechanism of action of PKIs (example of imatinib on PDGFR and BCR-ABL)

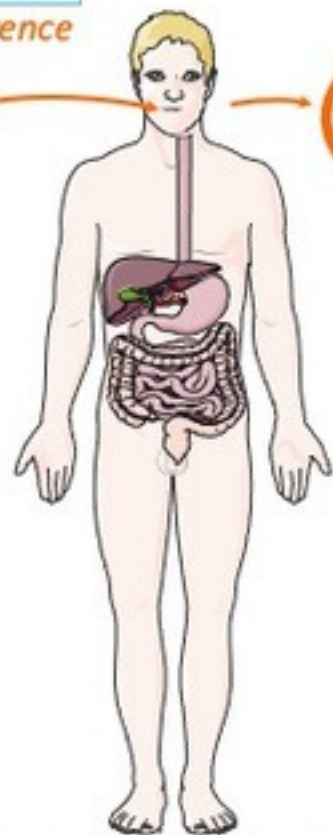
Figure 2. Factors influencing the pharmacokinetics of TKIs (from [6], with kind permission of © La Lettre du Pharmacologue 2010;24(4):122.).

In blue: pharmacokinetic phases of TKIs. In orange: associated factors that may modify them.



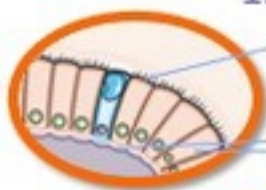
Dose

Adherence



*Age, sex, weight and
body surface, ethnicity,
Polymorphisms,
pathologies, etc...*

1. Absorption:
food



Transporters

Influx (Ex: Oct-1)

Efflux (Ex: p-gp)

Drug Interactions



2. Metabolism: CYP450 3A4, ...



3a. Distribution: *protein binding*
(Albumin, AGP)



3b. Cells diffusion:
vascularisation, necrosis,



4. Elimination:
*Hepatic insufficiency
Renal failure*

Clinical
Response