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Metabolism-related pharmacokinetic drug–drug interactions with tyrosine kinase inhibitors: current understanding, challenges and recommendations

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Drug–drug interactions (DDIs) occur when a patient's response to the drug is modified by administration or co-exposure to another drug. The main cytochrome P450 (CYP) enzyme, CYP3A4, is implicated in the metabolism of almost all of the tyrosine kinase inhibitors (TKIs). Therefore, there is a substantial potential for interaction between TKIs and other drugs that modulate the activity of this metabolic pathway. Cancer patients are susceptible to DDIs as they receive many medications, either for supportive care or for treatment of toxicity. Differences in DDI outcomes are generally negligible because of the wide therapeutic window of common drugs. However for anticancer agents, serious clinical consequences may occur from small changes in drug metabolism and pharmacokinetics. Therefore, the objective of this review is to highlight the current understanding of DDIs among TKIs, with a focus on metabolism, as well as to identify challenges in the prediction of DDIs and provide recommendations.

Introduction

Tyrosine kinases are a major family of proteins frequently dysregulated (either through somatic mutations or over-expression) in various cancers. Their critical role in the control of cancer phenotypes, coupled to the presence of suitable binding domains for small molecules, led to the development of many tyrosine kinase inhibitors (TKIs) as anti-cancer agents. As we are able to achieve a better control of the disease over the longer lifespan of a patient, these TKIs are now being considered as chronic medications as they are used over a long period of time. The increasing number of therapies has improved the prognosis for the disease but has augmented the challenge of evaluating patients for potential drug interactions during therapy [1].

Drug–drug interactions (DDIs) occur when a patient's pharmacological or clinical response to the drug is modified by administration or co-exposure to another drug. Pharmacokinetic interactions occur when one drug influences the pharmacokinetic processes such as absorption, distribution, metabolism and excretion, of another drug. Altered metabolism is among the most complex of these processes by which drug–drug interactions can occur, and induction or inhibition of hepatic enzymes by drugs are often implicated. The clinical consequences of enzyme induction or inhibition depend on the pharmacological and toxic effect of both the parent drug and its

metabolite(s). For example, if the parent compound is more active than its metabolite, inhibition of metabolism increases the exposure to the drug and also its therapeutic and/or toxic effects. However, if the parent compound is a pro-drug, inhibition of metabolism may result in a decrease in therapeutic efficacy. More recently, another paradigm of interaction arises when the metabolite is more toxic, and hence induction of metabolism down this pathway can exacerbate toxicity.

Central to the metabolism of drugs is the cytochrome P450 (CYP) family of enzymes. This consists of numerous enzymes that are responsible for the phase I metabolism of many drugs, nutrients, endogenous substances, and environmental toxins. The main CYP enzyme, CYP3A4, is responsible for the metabolism of more than 50% of all drugs in the market. It is also implicated in the metabolism of almost all of the TKIs. Therefore, there is a substantial potential for interaction between TKIs and other drugs that modulate the activity of this metabolic pathway.

A recent study revealed that co-prescription of drugs that induce or inhibit metabolic pathways used by TKIs was high. Overall co-prescribing rates for DDI drugs that may decrease TKIs effectiveness ranged from 23–57%, while co-prescribing rates with drugs that may increase TKI toxicity ranged from 24–74% [2]. In another study which studied the pattern of DDIs in cancer patients, the frequency of at least one potential DDI occurring was 63%. Among them, almost 62% of the identified DDIs were considered as major, where the effects of the interaction may result in serious consequences such as hospitalization, therapeutic failure, permanent injury or even death [3]. Although many studies highlighted the problem of frequent DDIs among TKIs, these studies did not address the clinical consequences of the potential DDIs, such as increased toxicity or therapeutic failure. In some cases, these combinations could have been intentionally prescribed, where physicians may have knowingly prescribed a potentially interacting combination because they considered the potential benefits to outweigh the risks or because the patient had tolerated the combination in the past [4]. As these TKIs are relatively new to the market, the scientific evidence that supports their DDI is limited. Therefore, it is not unexpected to observe that oncology professionals are unable to identify TKI DDI pairs which that might have a high probability of causing deleterious effects in cancer patients [5].

Cancer patients are susceptible to DDIs as they receive many medications, either for supportive care or for treatment of therapy-induced toxicity [6]. For instance, an observational study highlighted that patients were receiving on average 6.8 drugs in addition to sunitinib. Among them, antihypertensive drugs were most commonly prescribed, followed by analgesics, anti-emetics and thyroid substitution therapy [7]. In certain cases, a cancer patient's pharmacokinetic parameters may be also altered, for example, oedema affecting volume of distribution or impaired drug absorption due to malnutrition or mucositis. These issues may also affect the consequences of DDIs. Since most cancers typically occur at a later age, these patients may also be receiving other drugs for the management of their comorbidities. Differences in DDI outcomes are generally negligible because of the wide therapeutic windows of common drugs. However, in cancer chemotherapy with anti-cancer drugs, serious clinical consequences may occur from small changes in drug metabolism and pharmacokinetics [8]. Studies conducted by our group have exhibited the increase in risk of toxicity as a consequence of DDIs [9]. Sunitinib, a multi-kinase inhibitor used in the first line treatment of metastatic renal cell carcinoma, has been associated with dose-limiting dermatological toxicities such as hand-foot skin reaction (HFSR), rash and dry skin [10]. Sunitinib undergoes metabolism by CYP3A4 to form an active metabolite, SU12662 (N-desethyl sunitinib). A recent study has demonstrated that sunitinib is more dermatotoxic than SU12662, suggesting that patients who receive concomitant CYP3A4 inhibitors would be at a higher risk of dermatological toxicities, due to a lower ability to metabolize sunitinib [11]. Consequently, this may result in an increased risk of non-compliance, dose reduction or therapy discontinuation, thereby leading to suboptimal therapy.

Due to the substantial potential for interaction between TKIs and other drugs that modulate the activity of metabolic pathways, unwanted clinical consequences may occur from small changes in drug metabolism and pharmacokinetics in cancer patients. Furthermore, it is a challenge to determine the clinical effects of the DDI due to the large inter-patient variability in the pharmacokinetics of the TKIs. Therefore, the objective of this review is to highlight the current understanding of DDIs among TKIs, with a specific focus on DDIs involving metabolism, and to identify challenges in the prediction of DDIs and provide some possible recommendations.

Methods

A search was conducted to identify all small molecule TKIs approved by the FDA from January 2000 to February 2014. A comprehensive literature search of articles involving TKIs was performed using the PubMed and Scopus databases. Meetings abstracts presented at the American Association for Cancer Research (AACR) and the American Society of Clinical Oncology (ASCO) were also reviewed. The search was conducted by using the generic names of all the identified TKIs (afatinib, axitinib, bosutinib, cabozantinib, crizotinib, dasatinib, erlotinib, gefitinib, imatinib, lapatinib, nilotinib, pazopanib, ponatinib, regorafenib, sorafenib, sunitinib, vandetanib), and terms such as 'drug interaction', 'metabolism' and

'pharmacokinetics'. The search was limited to English language articles published between January 1995 and February 2014.

Results and discussion

Overview of TKIs (Table 1)

There are currently 17 FDA-approved TKIs (as of 31 March 2014) and they are indicated for various malignancies ranging from solid tumours such as breast and lung cancers to haematological malignancies like chronic myeloid leukemia.

Metabolism profile of TKIs (Table 2)

Almost all of the TKIs undergo metabolism by CYP enzymes. CYP3A4 is the CYP enzyme involved in the metabolism of the majority of the TKIs. Some of these TKIs, including imatinib, sunitinib and dasatinib, form an active metabolite upon metabolism. These TKIs can also act as an inducer or inhibitor to the CYP enzymes. All TKIs are primarily excreted in the faeces. However, the percentage of unchanged drug recovered in the faeces and urine varies widely between the TKIs. This could be likely due to the varying degree of absorption of the drug or due to differences in the extent of drug metabolism.

Potential effect of enzyme inducers/inhibitors on the pharmacokinetics of TKIs (Table 3)

As most of these TKIs are substrates of the CYP3A4 enzyme, inducers and inhibitors of this enzyme can affect the exposure to these TKIs. The most common inducer and inhibitor used for the study of the potential pharmacokinetic interaction are rifampicin and ketoconazole, respectively. As expected, ketoconazole increases the exposure of TKIs due to the inhibition of metabolism. However, the extent to which the exposure is increased varied widely between the TKIs. For instance, concomitant ketoconazole can result in a slight increase of imatinib area under the curve (AUC) by 40% [12] but for bosutinib, the increase in AUC is more than eight

Table 1

Overview of FDA-approved TKIs

	Year of FDA approval	Indication(s)	Targets	FDA black box warning	Dosing administration	Reference
Afatinib (Gilotrif)	2013	Metastatic NSCLC with EGFR mutations	EGFR, HER2, HER4		40 mg once daily	[52]
Axitinib (Inlyta)	2012	Advanced RCC	VEGFR-1, VEGFR-2, and VEGFR-3		5 mg twice daily	[53]
Bosutinib (Bosulif)	2012	CML	Bcr-Abl, Src		500 mg once daily	[16]
Cabozantinib (Cometriq)	2012	Thyroid cancer	RET, MET, VEGFR-1, –2 and –3, KIT, TRKB, FLT-3, AXL, and TIE-2	Haemorrhage	140 mg once daily	[54]
Crizotinib (Xalkori)	2011	ALK+ NSCLC	ALK, MET, RON		250 mg twice daily	[55]
Dasatinib (Sprycel)	2006	CML Ph+ ALL	Bcr-Abl, Src		100 mg once daily	[56]
Erlotinib (Tarceva)	2004	NSCLC Metastatic pancreatic cancer	EGFR		100–150 mg once daily	[57]
Gefitinib (Iressa)	2003	NSCLC	EGFR		250 mg once daily	[58]
Imatinib (Gleevec)	2001	CML GIST Ph+ ALL	Bcr-Abl		300–800 mg once daily*	[59]
Lapatinib (Tykerb)	2007	Metastatic breast cancer	EGFR, HER2	Hepatotoxicity	1250–1500 mg once daily*	[60]
Nilotinib (Tasigna)	2007	CML	Bcr-Abl	QT prolongation	300 mg twice daily	[61]
Pazopanib (Votrient)	2009	RCC Soft tissue sarcoma	VEGFR-1, VEGFR-2 and VEGFR-3	Hepatotoxicity	800 mg once daily	[62]
Ponatinib (Iclusig)	2012	CML Ph+ ALL	Bcr-Abl	Arterial thrombosis and hepatotoxicity	45 mg once daily	[63]
Regorafenib (Stivarga)	2012	Metastatic colorectal cancer GIST	VEGFR2 and TIE2	Hepatotoxicity	160 mg once daily	[64]
Sorafenib (Nexavar)	2005	RCC Unresectable HCC	KIT, FLT-3, VEGFR-2, VEGFR-3 and PDGFR-B		400 mg twice daily	[65]
Sunitinib (Sutent)	2006	RCC GIST pNET	PDGFR (α,β) VEGFR (1, 2, 3), KIT, FLT3, CSF-1R, RET	Hepatotoxicity	37.5–50 mg once daily*	[66]
Vandetanib (Caprelsa)	2011	Thyroid Cancer	EGFR, VEGFR, RET	QT prolongation	800 mg once daily	[67]

*Dosing administration depends on indication. ALK+, anaplastic lymphoma kinase; ALL, acute lymphoblastic leukemia; CML, chronic myeloid leukemia; FDA, Food and Drug Administration; GIST, gastrointestinal stromal tumour; HCC, hepatocellular carcinoma; NSCLC, non-small-cell lung cancer; Ph+ ALL, Philadelphia chromosome-positive acute lymphoid leukemia; pNET, progressive, well-differentiated pancreatic neuroendocrine u; RCC, renal cell carcinoma.

Table 2

Metabolism profile of FDA-approved TKIs

	% of dose recovered (% recovered unchanged)		Metabolism			
	Feces	Urine	Major CYPs	Minor CYPs & others	Induces	Inhibits
Afatinib	85 (NR)	4 (NR)		Negligible		
Axitinib	41 (12)	23 (ND)	CYP3A4 CYP3A5	CYP1A2 CYP2C19 UGT1A1		CYP1A2 CYP2C8
Bosutinib	91 (NR)	3 (NR)	CYP3A4			
Cabozantinib	54 (NR)	27 (NR)	CYP3A4	CYP2C9	CYP1A1	CYP2C8 CYP2C9 CYP2C19 CYP3A4
Crizotinib	63 (53)	22 (2)	CYP3A4 CYP3A5			CYP3A CYP2B6
Dasatinib	85 (19)	4 (<1)	CYP3A4	FMO-3 UGT		CYP3A4
Erlotinib	83 (1)	8 (<1)	CYP3A4	CYP1A2 CYP1A1		CYP1A1 CYP3A4 CYP2C8
Gefitinib	86 (NR)	4 (NR)	CYP3A4 CYP2D6			CYP2C19 CYP2D6
Imatinib	68 (20)	13 (5)	CYP3A4	CYP1A2 CYP2D6 CYP2C9 CYP2C19		CYP2C8 CYP2C9 CYP3A4/5 CYP2D6
Lapatinib	(27)	(<2)	CYP3A4 CYP3A5	CYP2C19 CYP2C8		CYP3A CYP2C8
Nilotinib	93 (69)	N.R.	CYP3A4	CYP2C8	CYP2B6 CYP2C8 CYP2C9	CYP3A4 CYP2C8 CYP2C9 CYP2D6
Pazopanib	Majority in faeces	4	CYP3A4	CYP1A2 CYP2C8		CYP1A2 CYP3A4 CYP2B6 CYP2C8 CYP2C9 CYP2C19 CYP2D6 CYP2E1
Ponatinib	87 (NR)	5 (NR)	CYP3A4	CYP2C8 CYP2D6 CYP3A5		
Regorafenib	71 (47)	19 (2)	CYP3A4	UGT1A9		CYP2C8 CYP2C9 CYP2B6 CYP3A4 CYP2C19
Sorafenib	77 (51)	19 (ND)	CYP3A4	UGT1A9		CYP2B6 CYP2C8 CYP2C9 CYP2C19 CYP2D6 CYP3A4
Sunitinib	61 (NR)	16 (NR)	CYP3A4			
Vandetanib	44 (NR)	25 (NR)	CYP3A4	FMO-1 FMO-3		

All information was obtained from product information labels [68, 69]. ND, not detected; NR, not reported.

times with concomitant ketoconazole [13]. It is also interesting to note that exposure to TKIs is much increased by concomitant ketoconazole, as CYP3A4 is the only enzyme involved in the TKI's metabolic pathway. This is also supported by a report by Scripture *et al*. whereby drug interactions are likely to be significant when drug elimination occurs primarily through a single metabolic pathway [14]. Similarly for rifampicin, the combination of

Table 3

Potential effect of enzyme inhibitors/inducers on the pharmacokinetics of TKIs

	Changes in PK of TKI	Recommendations	Reference
Afatinib	Unlikely	Unlikely	[52]
Axitinib	Ketoconazole: ↑ 1.5× C_{max}, ↑ 2× AUC of axitinib	Strong 3A4/5 inhibitors → Avoid; Consider alternative agents; Consider ↓ dose of axitinib by half	[53, 70, 71]
	Rifampicin: ↓ 71% C_{max}, ↓ 79% AUC of axitinib	Strong 3A4/5 inducers → Avoid; Consider alternative agents	
Bosutinib	Ketoconazole: ↑ 5.2× C_{max}, ↑ 8.6× AUC of bosutinib	Strong 3A inhibitors → Avoid	[13, 16]
	Rifampicin: ↓ 86% C_{max}, ↓ 94% AUC of bosutinib	Strong 3A inducers → Avoid	
Cabozantinib	Ketoconazole: ↑ 38% AUC of cabozantinib	Strong 3A4 inhibitors → Avoid; Consider ↓ daily dose of cabozantinib by 40 mg	[54]
	Rifampicin : ↓ 77% AUC of cabozantinib	Strong 3A4 inducers → Avoid; Consider ↑ daily dose of cabozantinib by 40 mg	
Crizotinib	Ketoconazole: ↑ 1.4× C_{max}, ↑ 3.2× AUC of crizotinib	Strong 3A4 inhibitors → Avoid	[55]
	Rifampicin: ↓ 69% C_{max}, ↓ 82% AUC of crizotinib	Strong 3A4 inducers → Avoid	
Dasatinib	Ketoconazole: ↑ 4× C_{max}, ↑ 5× AUC of dasatinib	Strong 3A4 inhibitors → Avoid; Consider alternative agents; Consider ↓ dose of dasatinib to 20 mg daily (for patients taking 100 mg) or 40 mg daily (for patients taking 140 mg)	[56, 72]
	Rifampicin : ↓ 81% C_{max}, ↓ 82% AUC of dasatinib	Strong 3A4 inducers → Consider alternative agents; Consider ↑ dose of dasatinib	
Erlotinib	Ketoconazole: ↑ 67% AUC of erlotinib Ciprofloxacin: ↑ 17% C_{max}, ↑ 39% AUC of erlotinib	Strong 3A4 inhibitors → Use with caution	[57]
	Rifampicin: ↓ 58% AUC of erlotinib	Strong 3A4 inducers → Consider alternative agents; consider ↑ dose of erlotinib (up to maximum of 450 mg)	
Gefitinib	Itraconazole: ↑ 51% C_{max}, ↑ 78% AUC of gefitinib	Strong 3A4 inhibitors → Use with caution	[22, 58, 73]
	Rifampicin: ↓ 65% C_{max}, ↓ 83% AUC of gefitinib	Strong 3A4 inducers → Consider ↑ dose of gefitinib to 500 mg daily	
	Phenytoin: ↓ 26% C_{max}, ↓ 47% AUC of gefitinib		
Imatinib	Ketoconazole: ↑ 26% C_{max}, ↑ 40% AUC of imatinib Gemfibrozil*: ↓ 56% C_{max}, ↓ 48% AUC of N-desmethylimatinib	Strong 3A4 inhibitors → Use with caution	[12, 59, 74–76]
	Rifampicin: ↓ 54% C_{max}, ↓ 74% AUC of imatinib EIAEDs: ↓ 68% C_{trough} of imatinib	Strong 3A4 inducers → Consider alternative agents	
Lapatinib	Ketoconazole: ↑ 114% C_{max}, ↑ 257% AUC of lapatinib	Strong 3A4 inhibitor → Avoid; Consider ↓ dose of lapatinib to 500 mg daily	[60, 77]
	Carbamazepine: ↓ 59% C_{max}, ↓ 72% AUC of lapatinib	Strong 3A4 inducers → Avoid; Consider ↑ dose of lapatinib up to 4500 mg daily (for HER2+ metastatic breast cancer) or 5500 mg daily (for HR+, HER2+ breast cancer)	
Nilotinib	Ketoconazole: ↑ 1.8× C_{max}, ↑ 3× AUC of nilotinib	Strong 3A4 inhibitors → Avoid; Consider ↓ dose of nilotinib to 300 mg daily (in resistant or intolerant Ph+ CML) or 200 mg daily (newly diagnosed Ph+ CML-CP)	[61, 78]
	Rifampicin: ↓ 64% C_{max}, ↓ 80% AUC of nilotinib	Strong 3A4 inducers → Avoid; Consider alternative agents	
Pazopanib	Ketoconazole: ↑ 45% C_{max}, ↑ 66% AUC of pazopanib	Strong 3A4 inhibitors → Avoid; Consider ↓ dose of pazopanib to 400 mg	[62, 79]
		Strong 3A4 inducers → Pazopanib should not be used	
Ponatinib	Ketoconazole: ↑ 47% C_{max}, ↑ 78% AUC of ponatinib	Strong 3A4 inhibitors → Consider ↓ dose of ponatinib to 30 mg daily	[63, 80]
Regorafenib	Ketoconazole: ↑ AUC of regorafenib	Strong 3A inhibitors → Avoid	[64]
	Rifampicin: ↓ AUC of regorafenib	Strong 3A4 inducers → Avoid	
Sorafenib	Ketoconazole: no change in AUC of sorafenib		[65]
	Rifampicin: ↓ 37% AUC of sorafenib	Strong 3A4 inducers → Consider ↑ dose of sorafenib	
Sunitinib	Ketoconazole: ↑ 49% C_{max}, ↑ 51% AUC of combined sunitinib and N-desethyl sunitinib	Strong 3A4 inhibitor → Consider alternative agents; Consider ↓ dose reduction of sunitinib to a minimum of 37.5 mg (GIST & RCC) or 25 mg (pNET)	[66, 81]
	Ritonavir†: ↓ 48% C_{max}, ↓ 40% AUC of N-desethyl sunitinib		
	Rifampicin: ↓ 23% C_{max}, ↓ 50% AUC of combined sunitinib and N-desethyl sunitinib	Strong 3A4 inducers → Consider alternative agents; Consider ↑ dose of sunitinib to a maximum of 87.5 mg (GIST & RCC) or 62.5 mg (pNET)	
	Efavirenz‡: ↑ 410% C_{max}, ↑ 390% AUC of N-desethyl sunitinib		
Vandetanib	Itraconazole: ↑ 9% AUC of vandetanib		[15, 67]
	Rifampicin: ↓ 40% AUC of vandetanib	Strong 3A4 inducers → Avoid	

*Gemfibrozil inhibits the CYP2C8-mediated formation of N-desmethylimatinib (equipotent metabolite of parent imatinib). †Ritonavir inhibits the CYP3A4-mediated formation of N-desethyl sunitinib (equipotent metabolite of parent sunitinib). ‡Efavirenz induces the CYP3A4-mediated formation of N-desethyl sunitinib (equipotent metabolite of parent sunitinib). AUC, area under the curve; C_{max}, maximum concentration; C_{trough}, trough concentration; EIAEDs, enzyme-inducing anti-epileptic drugs; GIST, gastrointestinal stromal tumour; Ph+ CML, Philadelphia chromosome-positive chronic myeloid leukemia; Ph+ CML-CP, Philadelphia chromosome-positive chronic myeloid leukemia in chronic phase; PK, pharmacokinetics; pNET, progressive, well-differentiated pancreatic neuroendocrine tumours; RCC, renal cell carcinoma; TKI, tyrosine kinase inhibitor.

drugs resulted in a decrease in exposure to the TKIs. However, the extent to which the exposure is decreased is not as large as that observed with ketoconazole. The decrease in TKI AUC ranged from 40% for vandetanib [15] to 94% for bosutinib [16]. Among all the TKIs, sorafenib seems to be an exception, where studies have consistently demonstrated that clinically important interactions between sorafenib and drugs metabolized primarily by CYPs 3A4, 2C19, or 2D6 are not expected [17, 18]. Although co-administration of sorafenib with capecitabine has been shown to result in a mild increase in capecitabine exposure, these findings were not statistically significant and the mechanism of interaction is unclear [19]. As strong CYP3A4 inducers and inhibitors generally cause a change in exposure, the concomitant use of such agents with TKIs is not recommended and should be avoided if possible. If such combinations must be used, manufacturers generally recommend that dose increase or decrease may be considered and that patients should be monitored closely following any changes in dosages.

Effect of TKIs as enzyme inducers/inhibitors on the pharmacokinetics of other drugs

While the effect of enzyme inhibitors or inducers (such as ketoconazole and rifampicin) on the pharmacokinetics of TKI has been extensively studied, the reciprocal effect of a TKI acting as an enzyme inducer or inhibitor has been comparatively less investigated. The ability for TKIs to increase or decrease plasma concentrations of non-anticancer drugs is mainly unclear, especially within *in vivo* conditions. Concomitant imatinib and simvastatin has resulted in a two-fold increase in simvastatin's maximum plasma concentration (C_{max}) and a three-fold increase in simvastatin AUC. This is likely due to inhibition by imatinib of the CYP3A4 enzyme, which is responsible for the metabolism of simvastatin to other metabolites. This also suggests that in the presence of imatinib, plasma concentrations of standard doses of drugs which are degraded by the CYP3A4 enzyme may also be increased. As such, caution is required when imatinib is administered with other CYP3A4 substrates with a narrow therapeutic window [20]. Imatinib has also been shown to increase the exposure to metoprolol (23% increase in metoprolol AUC) when both agents are used together, due to the inhibition of the CYP2D6 enzyme by imatinib [21]. Although the combination of gefitinib and metoprolol also resulted in an increased exposure to metoprolol (35% increase in metoprolol AUC), this change was not statistically significant. Despite this, gefitinib has a potential to increase plasma concentrations of CYP2D6 substrates and caution should be exercised when using CYP2D6 substrates that have a narrow therapeutic window [22]. Concomitant use of two TKIs has also been investigated in certain cases. Clearance of erlotinib was markedly enhanced by sorafenib when the two agents were given concurrently, although the potential mechanism for this seeming interaction is not obvious [23]. In another example, co-administration of lapatinib and pazopanib led to an increase in pazopanib exposure, and it has been suggested that this might be the result of inhibition of CYP3A4 and/or cellular transporters such as ABCB1 and ABCG2 by lapatinib [24]. The effect of lapatinib on the clearance of vinorelbine has also been studied, where lapatinib resulted in a lower clearance of vinorelbine due to the inhibition of CYP3A4 [25].

Applicability of in vitro *and* in vivo *data within clinical practice*

The majority of the available pharmacokinetic information results from *in vitro* data, preclinical animal studies or from small phase I studies which evaluated healthy volunteers who were administered a single dose of the drugs. Emerging methods include creating a simulator where *in vivo* clearances can be predicted from their *in vitro* data. For instance, the impact of co-administration of ketoconazole was simulated and the predicted two-fold increase in erlotinib exposure was found to be consistent with the results of a clinical study [26]. However, in most cases, the prediction may not be entirely accurate, especially when most of these studies evaluate DDIs in the form of two interacting drugs, and these results may not be realistic where multiple drugs are used concurrently. In addition, several reasons have been proposed to highlight the inability of clinical interactions to be predicted accurately. Firstly, it is not always possible to determine the therapeutic concentration of a new drug and its metabolites in specific tissues. To complicate the issue further, the multiplicity of enzymes and transporters involved in the disposition of the said drugs and the intricacy of the pathways and interactions, in addition to overlapping substrate specificities of these proteins, results in complex and sometimes perplexing pharmacokinetic interactions with multidrug regimens. Large differences in genotype and expression level of each of these contributors can lead to a very complex influence on actual drug disposition. There can also be compensatory responses when one enzyme or transporter is inhibited, 'cushioning' any resulting change in metabolism. Each drug has a different level of dependence on intrinsic clearance for its overall clearance. Drugs with a high extraction ratio may be less sensitive to enzyme inhibition and induction, as their clearance is limited by blood flow rather than intrinsic activity. This makes it very challenging to test all of them in an *in vitro* system. Furthermore, the clinical significance of an interaction is unknown even if the *in vitro* or *in vivo* effect was established. Moreover, underlying disease states may influence the occurrence of an interaction that is unaccounted for by *in vitro* studies or by studies involving healthy volunteers alone [27, 28]. Endogenous CYP isoforms expressed in tumour cells also contributes to the metabolism of active drug, thereby playing a role in

altering the half-life and kinetics of the administered TKI [29]. In summary, it is complex and challenging to extrapolate these preliminary results to routine clinical practice, where TKIs are used to treat patients with cancer, many of whom are receiving multiple drugs and many of whom have impaired renal or hepatic function [30].

Formation of reactive intermediates/metabolites and implications for toxicity

Several TKIs such as dasatinib, erlotinib, gefitinib, imatinib, lapatinib, nilotinib, pazopanib, sorafenib and sunitinib undergo bioactivation to form reactive intermediates, which has implications in the generation of idiosyncratic adverse drug reactions (ADR) [31]. One TKI whose metabolism and implications for toxicity has been extensively studied is lapatinib. Lapatinib has been shown to be extensively metabolized, as exemplified by diverse biotransformations to form metabolites. A number of the metabolites could potentially form reactive electrophilic intermediates that could contribute to hepatotoxicity [32]. It is also worthy of note that the daily dose of these TKIs is high. For example the daily dose of lapatinib is more than 1000 mg. A high daily dose of more than 50 mg has been demonstrated to be a risk factor for ADRs [33]; thereby setting 13 out of the 17 approved TKIs at risk. Due to the high dose, there would be high amounts of these reactive intermediates or metabolites generated, thus increasing the risk for toxicity [34]. A recent study also further demonstrates that a dose more than 100 mg daily and being a substrate of CYP450 enzymes are two important predictors of drug-induced liver injury [35].

Actual drug–drug interaction cases involving TKIs as documented in the literature (Table 4)

There have been several reports demonstrating actual DDI cases in clinical practice. The events reported were potentially fatal ones such as hepatotoxicity and anticoagulation abnormalities. The concomitant use of imatinib and voriconazole resulted in markedly elevated concentrations of imatinib (between 3500–4700 ng ml^{-1}), than compared with when imatinib was used alone (2000 ng ml^{-1}). The raised plasma concentrations resulted in severe pustular eruption in the patient, and this was deemed due to the inhibition of imatinib metabolism by voriconazole [36]. Transaminase elevations have also been observed in drug pairs involving pazopanib and simvastatin. As both drugs are substrates of the same enzymes and transporters, it is plausible that the concomitant administration of pazopanib and statins may alter systemic and/or hepatic exposures, leading to increased toxicities such as liver injury [37]. In a study implicating interaction between lapatinib and dexamethasone, both *in vitro* and clinical results points to the increased risk of hepatotoxicity when the combination of drugs was used together. It has been proposed that the concomitant use may cause an increase in the metabolism of lapatinib by dexamethasone, thereby increasing the formation of lapatinib-derived reactive metabolites, and leading to toxicity [9]. However, this list of DDI cases is not exhaustive as there remains a possibility that many DDI cases remains unreported in the literature. Even if the drug pair is not listed in this table, it does not indicate that it is entirely safe for use. Healthcare professionals should still be aware of the potential interactions that may occur, and be vigilant in monitoring those patients who are receiving any potentially-interacting drug pairs.

Challenges

The large amount of published research into drug interactions might have overwhelmed most healthcare practitioners. As a clinician cannot know all potential clinically significant drug interactions, this emphasizes the need for practical identification and management systems [6]. The inefficiency of updating and maintaining drug labels poses a serious threat to patients. For example, despite the recent evidence supporting a larger contribution of CYP2C8 and a less significant role for CYP3A4 in the metabolism of imatinib, drug labels continue to warn against potential interactions with CYP3A4 inhibitors but fail to mention any risk with a CYP2C8 inhibitor [38]. Few databases and software programs are capable of checking for all potential interactions among multiple medications. More importantly, the absence of reported interactions does not guarantee a lack of interaction [39].

Recommendations

The majority of the phase I trials have evaluated two drug combinations of therapeutic interest, rather than combinations hypothesized to have a DDI. When DDI studies were performed with a clear rationale, the probability of identifying a DDI increased from 8% to 32%. This demonstrates the importance of understanding the mechanism behind a DDI and the value to which this translates clinically and suggests that DDI studies should only be performed when there is a pre-specified plausible hypothesis [40].

Most pharmacokinetic studies would report changes in TKI exposure as a result of the enzyme inhibitor or inducer. However it would be useful if the investigators also provided information regarding its potential effect on toxicity or efficacy [41].

It is imperative that comprehensive and accurate information be collected on the use of medications by patients, to increase awareness and familiarity with potential DDIs to ensure patient safety and to aid the development of optimal therapy [42, 43]. To reduce the potential for unexpected drug interactions during therapy, the patient's medical history should be taken thoroughly and interactively, and updated periodically [1]. Patients who have risk factors for potential DDIs should also be monitored more closely. Risk factors for potential DDI include liver function

Table 4

Actual drug–drug interaction cases involving TKIs as documented in the literature

TKI	Interacting drug	Event	Remarks	Recommendations	Reference
Gefitinib	Anastrozole	Liver toxicity		Routinely monitor liver transaminases in all patients treated with gefitinib	[82]
	Warfarin	Coagulation abnormalities (Prothrombin time [PT] and international normalized ratio [INR] abnormalities)	Gefitinib could inhibit the metabolism of warfarin, which is a substrate of CYP1A2, CYP2C9, and CYP3A4. The degree of the inhibitory effect of gefitinib on CYP enzymes varies from patient to patient. This may in part explain the variability of the PT-INR values observed on the coadministration of gefitinib and warfarin	Close monitoring of PT-INR is recommended for patients receiving gefitinib and warfarin, especially during the first 2 weeks after the beginning of warfarin therapy. Appropriate adjustment of the warfarin dose should be done if an altered response to warfarin is observed.	[83]
Imatinib	Voriconazole	Severe pustular eruption	Plasma concentrations of imatinib markedly elevated during simultaneous administration with voriconazole, possibly due to inhibition of imatinib metabolism by voriconazole	Use of imatinib in association with CYP3A4 inhibitors has to be considered with caution. When such an association is considered, the monitoring of imatinib plasma levels in patients may be of help for identifying individuals with high imatinib concentrations who are at risk of developing toxicity, including skin lesions.	[36]
	Amlodipine	Peripheral neuropathy	Amlodipine inhibits CYP3A4, which could increase imatinib concentrations	Therapeutic monitoring of plasma imatinib levels may be useful to investigate unexpected imatinib toxicity.	[84]
	Phenytoin		AUC of imatinib was decreased by about 80%. After phenytoin was discontinued and the imatinib dose was increased to 500 mg daily, a complete haematological response was observed.	–	[85]
	Levothyroxine	Hypothyroidism	Mechanism unclear	Evaluate thyroid function in hypothyroid patients on tyrosine kinase inhibitors	[86]
Lapatinib	Dexamethasone	Hepatotoxicity	Concomitant use may cause an increase in metabolizing capacity by dexamethasone, which in turn increases the formation of lapatinib-derived RM thereby elevating the risk of toxicity	Clinicians should be aware of this risk when considering the use of this combination and follow through with close monitoring where necessary.	[9]
Pazopanib	Simvastatin	Transaminase elevations	As pazopanib and statins are substrates for the same key metabolizing enzymes e.g. CYP3A4 and drug transporters, it is plausible that concomitant administration of pazopanib and statins may alter their systemic and/or hepatic exposures, leading to increased toxicities such as liver injury	In addition to implementing the recommended dose modification guidelines for pazopanib, discontinuation of simvastatin should be considered to manage the risk of liver injury in cancer patients receiving both medications	[37]
Sorafenib	Prednisolone		Serum concentration of sorafenib was gradually increased following tapering of prednisolone, possibly due to prednisolone inducing sorafenib metabolism	Therapeutic drug monitoring could be useful during sorafenib therapy in combination with prednisolone and for determining the optimal dosage of sorafenib.	[87]
Sunitinib	Levothyroxine	Hypothyroidism	Mechanism unclear	Evaluate thyroid function in hypothyroid patients on tyrosine kinase inhibitors	[86]

status, age, tumour type [44], number and type of medications received [45] and using drugs that are metabolized exclusively by only one CYP isoform [46].

When drugs with potential DDIs are considered for use with TKIs, clinicians should also consider alternative agents that have no or less interaction potential. However, it is also important to note that in some cases, switching to an alternative agent does not have any significant difference on the pharmacokinetic profile. For instance, despite azithromycin having a low potential for interaction, there was no significant effect of oral clarithromycin or azithromycin on the pharmacokinetic profile of sunitinib after single administration [47]. Because we do not know the clinical effects of these potential interactions when drugs with potential DDIs need to be used with TKIs (e.g. in cases where there is a compelling indication for the potential interacting drug to be used), more intense patient monitoring for interactions is needed. Scripture *et al*. have provided a valuable summary of the conditions where drug interactions are likely to be clinically significant, such as when drug elimination occurs primarily through a single metabolic pathway or when one or both of the interacting drugs has a steep dose–response curve or a narrow therapeutic range etc [14].

Utilization of therapeutic drug monitoring (TDM) in DDIs

The prerequisites of being a candidate for therapeutic drug monitoring (TDM) in clinical practice include long term therapy, significant inter-individual but limited intra-individual PK variability, narrow therapeutic index, a well-defined exposure–response (efficacy/toxicity) relationship and availability of appropriate bio-analytical methods for quantification [48–51]. As most of the TKIs fulfil the traditional criteria for a TDM programme, the role of TDM in TKI therapy is increasingly being studied. Furthermore, as TKIs have the potential to be involved in multiple interactions (e.g. drug–drug, drug–food and drug–herb) involving pharmacokinetic or pharmacodynamic pathways, TDM could complement clinical evaluation by providing additional information on efficacy, adherence and toxicity [51].

The application of TDM may be useful in DDIs for several reasons: for monitoring of patient when high risk drug pairs cannot be avoided, for diagnosis of DDIs and for dose adjustments [49]. In such cases, the changes in drug concentrations, together with the patient's response and toxicity, could be used together to make an informed decision, on whether the drug pair can be continued safely or whether dose adjustments should be performed. For example, in a recent study conducted by our group, we have demonstrated that sunitinib is more dermatotoxic than its active metabolite, SU12662 [11]. If sunitinib is used concomitantly with a CYP3A4 inducer, the total effective plasma concentration (sunitinib and SU12662) may still be above the therapeutic target. However, patients may experience less toxicity due to the lesser accumulation of the parent drug.

Although TDM of TKIs is still in its infancy, there is increasing evidence that dose adjustments based on pharmacokinetic targets would help to increase efficacy and reduce toxicity of TKIs, and might be beneficial for patients treated with most of the TKIs [50]. Currently, target plasma concentrations of TKIs and their respective dose-adaptation strategy are only available for several of the FDA-approved TKIs. Recommended therapeutic targets for efficacy are available for crizotinib, erlotinib, gefitinib, imatinib, nilotinib, pazopanib and sunitinib, and targets for safety are available for dasatinib and sunitinib [50]. Thus, application of TDM may be limited to those TKIs which have a recommended target and may be challenging in those TKIs which have a lack of information. Although there are recommended therapeutic targets available for some of the TKIs, no prospective studies have been conducted to validate these targets, and thus applications of TDM may best be reserved for individual situations relating to a lack of therapeutic response, severe or unexpected toxicities, drug–drug interactions or treatment adherence [51]. In summary, future research should focus on the role and benefits of TDM in TKI therapy, especially those with a well-established dose–response relationship and well-established pharmacokinetic targets. Prospective, randomized studies should be performed to confirm the benefits of implementation of TDM, such as reductions in toxicity and/or improvement in outcomes.

Summary and recommendations

As we are able to achieve a better control of the disease over the longer lifespan of a patient, TKIs are now being considered as chronic medications taken in an outpatient setting. Due to the large inter-patient variability in pharmacokinetics of these TKIs, any potential DDI could have serious consequences in a patient's therapy. Thus far, there have been numerous phase I and *in vitro* studies conducted to evaluate DDIs. This information has been incorporated into drug labels or drug information databases, to warn prescribers of the risk of such DDIs. However, as previously mentioned, it is somewhat challenging to extrapolate results from phase I and *in vitro* studies to routine clinical practice. During the drug development phase, potentially clinically relevant drug interactions are not usually detected. Only after receiving regulatory approval and after widespread usage, would a new DDI typically surface. Therefore, healthcare professionals, especially physicians and pharmacists, play a vital role in identifying these new interactions. Perhaps scheduled drug utilization reviews could be conducted routinely to identify any common DDI pairs. Prospective data could

then be collected regarding these DDI pairs, to identify any increase in toxicity or lack of efficacy events. Where possible, investigators could also subsequently recreate the interaction in an *in vitro* system to determine the mechanisms which may be involved. However, such research takes time and in the meantime, suspected DDI pairs would have to be used cautiously in patients. Nevertheless, using both clinical and *in vitro* data to validate claims of potential DDIs would ensure accuracy of data as well as clinical relevance. The utilization of TDM in DDIs may be useful when high risk drug pairs cannot be avoided, especially during initiation of therapy or when there is lack of response or occurrence of severe toxicities. Instead of withholding a beneficial drug therapy from a patient, the high risk drug pair may be continued safely with regular monitoring if the patient is not experiencing excessive toxicity, even when the drug concentrations are increased. In these situations, using additional information on drug concentrations together with patient's response and toxicity data, a more informed decision can be made.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

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