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Tyrosine kinases inhibitors: interactions and safe use

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Abstract

Tyrosine kinases inhibitors (TKI) are small molecules that interfere with cell signalling and target selected malignancies. The concern associated with oral drugs is related to their low and unpredictable bioavailability. In the past years, several TKI have been introduced in oncology and the risk of serious drug-drug interactions is very important and deserves to be taken into consideration. It is difficult to find a concise tool to help oncologists with this matter and this could create issues in the daily clinic.

This article gives a brief overview of known or suspected interactions either with other drugs or foods. Oncologists should carefully review the concomitant medications for each patient in order to prevent any relevant interactions or to monitor them closely.Â

Introduction

Tyrosine kinases inhibitors (TKI) are small molecules, orally administered that interfere with cell signalling and allow target-specific treatment for selected malignancies. Patientsâ€™ preference for oral treatment is well known and from the medical perspective, although it could be perceived as an advantage, the concern is that oral drugs may have low and unpredictable bioavailability. This could be due to variable degradation in gastrointestinal system, intestinal P-glycoprotein and interaction with cytochrome P450 (CYP3A4) catalytic activity which varies as much as 10-fold among individuals.

In the past years, several TKI have been introduced in oncology. These agents are currently extensively used and serious drug-drug interactions are a high risk event.

This article gives a brief overview of known or suspected drug-drug interactions between TKI and other drugs. Most interactions are related to metabolism by cytochrome P450 isoenzymes, altered stomach pH and prolongation of the QTc interval. The data are presented in tables.

Oncologists should carefully review the concomitant medications for each patient in order to prevent any relevant interactions or to monitor closely them.

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Cytochrome P450 and family

Table 1: Cytochrome P450, family 3, subfamily A (CYP3A4/5) inhibitors and inducers

inhibitors Â	Â	may **increase** plasma concentrations	**Â**	**inducers** Â	Â	may **reduce** plasma concentrations	Â
strong	Â	Ketoconazole Itraconazole Voriconazole Â	Avoid concomitant use or dose adjustment or monitoring	**strong**	Â	Rifampicin Rifabutin Rifapentin	Avoid concomitant use or dose adjustment or monitoring
	Â	Clarithromycin			Â	Dexamethasone	
	Â	Atazanavir Indinavir Nefazodone Nelfinavir Ritonavir Saquinavir			Â	Phenytoin Carbamazepine Phenobarbital Topiramate	
	Â	Nefazodone			Â	Hypericum perforatum [St. John's wort])	
Moderate	Â	Diltiazem Verapamil Amiodarone	Â	**Unspecified potency**	Â	Modafinil	Â
	Â	Aprepitant			Â	Capsaicin	
	Â	Bicalutamide			Â	Pioglitazone Troglitazone	
	Â	Erythromycin			Â	Â	
	Â	Grapefruit			Â	Â	
	Â	Valerian			Â	Â	
Weak	Â	Valproic			Â	Â	

QT interval

Table 2: Drugs which prolong QT interval

Â **Antisickness**	Onsansetron Domperidone
Â **Antidepressants**	Fluoxetine Trazodone Citalopram
Â **Â** **Antiarrhythmics**	Flecainide Quinidine Procainamide Sotalol Amiodarone
Â **Antifungal**	Fluconazole Voriconazole
Hormonal therapy	Gosereline
Opioids	Methadone
B2 agonists	Salmeterol
Alpha-blockers	Alfuzosin
Â **Â** **Antibiotics**	Azithromycin Ciprofloxacin Clarithromycin Erythromycin
Â **Antipsychotics**	Chlorpromazine Haloperidol

Â Antimalarial	Chloroquine Quinine

CYP3A substrates

Table 3: CYP3A substrates

Antifungals	Ketoconazole Itraconazole
Antibiotics	Clarithromycin Erythromycin Â
Antidepressants	Mirtazapine Venlafaxine Trazodone Sertraline Citalopram Norfluoxetine Amitryptiline
Antipsychotics	Haloperidol
Opioids	Buprenorphine Codeine Fentanyl Methadone Tramadol Alfentanil
Benzodiazepines and hypnotics	zopiclone alprazolam zolpidem midazolam diazepam
Statins	Atorvastatin Simvastatin
Calcium chanel blockers	nifedipine Diltiazem Verapamil
Antiemetics	aprepitant Domperidone ondansetron
Steroids	dexamethasone hydrocortisone
Proton pump inhibitor	Omeprazole
Antiplatelets	Clopidogrel
Beta agonists	Salmeterol
Stimulants	Caffeine
Protease inhibitors	Indinavir Ritonavir
H1 receptor antagonists	Chlorphenamine
PDE5 inhibitors	Sildenafil
antiarrhythmics	Amiodarone

P-glycoprotein (PgP)

Table 4: Drugs and P-glycoprotein (PgP)

Substrates	Inhibitors	Inducers
Colchicine	Verapamil	Carbamazepine
Digoxin	Amiodarone	Rifampicin
Morphine	Clarithromycin	St Johnâ€™s Wort
Indinavir	Erythromycin	Â
Â	Ketoconazole	Â
Â	Quinidine	Â

Drugs interacting with CYP3A substrates, inhibitors, inducers and PgP

Table 5: Drugs interacting with CYP3A substrates

Â CYP3A substrates	**Crizotinib**
	Dabrafenib
	Lenvatinib
	Imatinib

Â

Table 6:Â Drug interactions with CYP3A inhibitors/inducers

Axitinib	**Â CYP3A4/5 inducers Â Â Â Â Â CYP3A4/5 inhibitors**	**Â Â Â Â Â Â Prolong QT interval**	**Â**
Cabozantinib			Crizotinib
Crizotinib			Â
Everolimus			
Gefitinib			
Imatinib			
Lapatinib			Lapatinib
Pazopanib			Â
Sorafenib			Sorafenib
Sunitinib			Sunitinib
Regorafenib			Â
Vemurafenib			
Â	Â		Vandetanib

Â

Table 7: Drugs interacting with PgP substrates

Â PgP substrates	**Lapatinib**
	Lenvatinib
	Sorafenib

Gastric pH

Table 8: Interactions with pump inhibitors and antiacids

Antiacids	Increase levels of TKI	Reduce levels of TKI	Observations
Omeprazole Â	Axitinib	Crizotinib	Â
		Gefitinib	
		Lapatinib	If taken regularly
		Pazopanib	To take 1 hour before or 2 h after quick antiacids and 2 h before or 10 h after antiH2
Â			
Ranitidine	Â	Pazopanib	
Â			
Others	Â	Pazopanib	
		Dabrafenib	Â
		Trametinib	

Anticoagulants

Table 9: Interactions with anticoagulants

Â	Warfarin	Option
Axitinib	no interactionÂ	**Â**
Cabozantinib	no interactionÂ Â	Â
Crizotinib	no interactionÂ Â	Â
Dabrafenib	Reduce warfarin exposure	Close monitoring
Gefitinib	Increase risk of bleeding	Close monitoring

Everolimus	no interactionÂ Â	Â
Imatinib	Not to use	Low molecular weight heparin
Lenvatinib	no interactionÂ Â	Â
Lapatinib	no interactionÂ Â	Â
Regorafenib	Increase risk of bleeding	Close monitoring
Sorafenib	Low risk	Â
Sunitinib	no interactionÂ Â	Â
Pazopanib	no interactionÂ Â	Â
Vandetanib	Possible interaction	Close monitoring Not to use dabigatran
Vemurafenib	Increase risk of bleeding	Close monitoring

Other interactions

Table 10: Other interactions

Â	**Increase**	**Decrease**	**No significant change**
Levels of midazolam	Crizotinib	Vemurafenib	Regorafenib
Â	Everolimus	Â	Sorafenib
	Lapatinib		Â
	Pazopanib		
Â			
Levels of oral contraception	Â	Vemurafenib Lenvatinib??	Â
Â			
Levels of statins	Imatinib	Â	Everolimus
Atorvastatin	Regorafenib		Â
Simvastatin	Pazopanib		
Â			
Bisphosphonates	Cabozantinib	Â	Â
	Sunitinib		
Â			
Metformin	Vandetanib	Â	Â
Â			
Digoxin	Crizotinib	Â	Regorafenib
Â	Lapatinib		
	Sorafenib		
	Vandetanib		
	Vemurafenib		
Â			
Dextromethorphan	Pazopanib	Â	Sorafenib

Method of administration

Table 11: Method of administration

Â	**As a whole**	**With food**	**Without food**	**Water**	**Other options**
Axitinib	**X**	**X**	**X**	**X**	**Â**
Cabozantinib	**X**	**Â**	**X**	**X**	**2 h before and 1 h after**
Crizotinib	**X**	**X**	**X**	**X**	**Â**
Dabrafenib	**X**	**Â**	**Â**	**X**	**1 h before or 2 after a meal**
Gefitinib	**X**	**Â**	**Â**	**X**	**Dissolve in half glass of water (20 min),Â drink immediately. Add more water and drink**
Everolimus	**X**	**X**	**X**	**X**	**Â**
Imatinib	**X**	**X**	**Â**	**X**	**Â**
Lenvatinib	**Â**	**Â**	**Â**	**X/apple juice**	**In 1 tablespoon for 10 min, stir for 3 min and drink**
Lapatinib	**X**	**Â**	**X**	**Â**	**1 h before or after a meal**
Regorafenib	**X**	**X** **Low fat**	**Â**	**X**	**Â**
Sorafenib	**X**	**X** **Low fat**	**X** **Â**	**X**	**Â**
Sunitinib	**X**	**X**	**X**	**X**	**Â**
Pazopanib	**X**	**Â**	**X**	**Â**	**1 h before or 2 h after**
Trametinib	**X**	**Â**	**Â**	**X**	**1 h before or 2 after a meal**
Vandetanib	**X**	**Â**	**X**	**X**	**disperse in half glass of water** **Before or after a meal**
Vemurafenib	**X** **Â**	**Â**	**Â**	**X**	**Â**

Conclusion

In the past decade, many TKI have been introduced in oncology as targeted therapies against different malignancies. Although they seem to be well tolerated, the risk of serious interactions exists and it is the oncologist's responsibility to know these in order to prevent any relevant issues, such as toxicities or lack of effectiveness due to reduced bioavailability.

This brief summary presented in Tables form, pretends to be an easy tool to consult in the routine practice to help doctors make quick decisions and manage correctly these medications.

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