e-*Blood*

Drug interactions with the tyrosine kinase inhibitors imatinib, dasatinib, and nilotinib

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Several cancer treatments are shifting from traditional, time-limited, nonspecific cytotoxic chemotherapy cycles to continuous oral treatment with specific protein-targeted therapies. In this line, imatinib mesylate, a selective tyrosine kinases inhibitor (TKI), has excellent efficacy in the treatment of chronic myeloid leukemia. It has opened the way to the development of additional TKIs against chronic myeloid leukemia, including nilotinib and dasatinib. TKIs are prescribed for prolonged periods, often in patients with comorbidities. Therefore, they are regularly co-administered along with treatments at risk of drug-drug interactions. This aspect has been partially addressed so far, calling for a comprehensive review of the published data. We review here the available evidence and pharmacologic mechanisms of interactions between imatinib, dasatinib, and nilotinib and widely prescribed co-medications, including known inhibitors or inducers of cytochromes P450 or drug transporters. Information is mostly available for imatinib mesylate, well introduced in clinical practice. Several pharmacokinetic aspects yet remain insufficiently investigated for these drugs. Regular updates will be mandatory and so is the prospective reporting of unexpected clinical observations. (*Blood*. 2011;117(8):e75-e87)

Introduction

Targeted cancer therapies have been designed to interact with particular proteins associated with tumor development or progression. Many of these agents are tyrosine kinases inhibitors (TKIs), targeting enzymes whose disregulated expression and activity are associated with various cancers.[1] The pioneer small-molecule TKI imatinib has revolutionized the treatment and prognosis of chronic myeloid leukemia (CML). Imatinib inhibits the tyrosine kinase Bcr-Abl,[2] a fusion oncoprotein resulting from the translocation t(9;22)(q34;q11),[3] which is associated with the characteristic Philadelphia chromosome,[2] a hallmark of chronic myeloid leukemia and of some acute lymphoblastic leukemias.[4]

However, some patients, especially those in the advanced phase of the disease, develop resistance to imatinib therapy, because of various mechanisms such as *BCR-ABL* gene amplification,[5] low imatinib absorption, or more frequently point mutations into the oncoprotein sequence.[6] Several new inhibitors have been developed with increased potency and a broader range of activity against imatinib-resistant mutants. In vitro studies have shown that nilotinib, an imatinib derivative, and dasatinib, structurally unrelated to imatinib, are, respectively, 20- and 300-fold more potent than imatinib against unmutated Abl[7] and are active against many imatinib-resistant Bcr-Abl mutants.[7]

TKIs are extensively metabolized by cytochrome P450 enzymes (CYP), whose activities are characterized by a large degree of interindividual variability.[8] Some TKIs are also substrates or inhibitors of the drug transporters P-glycoprotein (Pgp; coded by *ABCB1*) Breast Cancer Resistance Protein (BCRP; *ABCG2*) and the organic cation transporter 1 (hOCT1; *SLC22A1*).[9-13] A standard regimen can therefore produce very different circulating and cell concentration profiles from one patient to another, thus favoring the selection of resistant cellular clones by subtherapeutic drug exposure or the occurrence of toxicity in case of overexposure.[14,15] Identifying the best active and safe dosing schedule for individual patients to maximize therapeutic benefit has become a scientific and clinical challenge. Combination therapies have been investigated in various conditions, which certainly add a level of treatment complexity, because overlapping toxicities and pharmacokinetic interactions have to be taken into consideration.[16,17]

We review here systematically and present under an easy-consulting form (Table 1) the information available on pharmacologic interactions between imatinib, dasatinib, and nilotinib and drugs concomitantly prescribed to patients receiving TKIs. The drugs were selected on the basis of the information extracted from our database, used within the framework of Therapeutic Drug Monitoring of TKIs.[15] Moreover, classical inhibitors or inducers of cytochromes P450 or drug transporters were also included in this review. We do not intend here to replace individualized medical evaluation, and the data presented here should be used in addition to thorough clinical judgment. Indeed, it may be that our searches still missed some interactions, and actually most interactions do not represent true contraindications but rather call for appropriate dosage adjustments and treatment monitoring measures.

Review of the literature

In addition to official monographs of the drugs,[9] literature from Medline and Evidence-Based Medicine Reviews was systematically searched, using the following MeSH terms: "Drug interactions," "Cytochrome

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Table 1 (in 10 parts) summarizes observed or potential drug interactions between TKIs and commonly concomitantly prescribed drugs or classical interacting agents (lines) sorted according to the ATC classification. The arrows ↑ and ↓ indicate an increase or decrease of drug concentration, respectively. Boldface text outlines interactions reported in the literature (reference number), whereas standard characters represent potential interactions predicted from theoretical considerations (but not yet reported in the literature). "Absence of interaction" means that a clinical study concluded to the absence of interaction (reference number), and "—" means that no interaction is either reported or theoretically expected.

Part 1. Alimentary tract and metabolism

	Imatinib	Dasatinib	Nilotinib
PPI			
Omeprazole	• Inhibition of Pgp by omeprazole: ↑ imatinib exposure[9,18,64]	• ↓ **dasatinib absorption**[9] (↓ dasatinib solubility) • Inhibition of Pgp by omeprazole: ↑ dasatinib exposure[9,18,64]	—
Esomeprazole	• Inhibition of Pgp by esomeprazole: ↑ imatinib exposure[9,18,64]	• ↓ **dasatinib absorption**[9] (↓ dasatinib solubility) • Inhibition of Pgp by esomeprazole: ↑ dasatinib exposure[9,18,64]	—
Pantoprazole	• Inhibition of Pgp by pantoprazole: ↑ imatinib exposure[9,18,64]	• ↓ **dasatinib absorption**[9] (↓ dasatinib solubility) • Inhibition of Pgp by pantoprazole: ↑ dasatinib exposure[9,18,64]	—
H2-antagonists			
Cimetidine	• Inhibition of CYP 3A4 and Pgp by cimetidine: ↑ imatinib exposure[18,65] • Inhibition of hOCT1 by cimetidine: ↓ imatinib intracellular exposure[18,64,65]	• ↓ **dasatinib absorption**[9] (↓ dasatinib solubility) • Inhibition of CYP 3A4 and Pgp by cimetidine: ↑ dasatinib exposure[18,65]	• Inhibition of CYP 3A4 by cimetidine: ↑ nilotinib exposure[18,65]
Ranitidine	• Inhibition of Pgp by ranitidine: ↑ imatinib exposure[18,65] • Inhibition of hOCT1 by ranitidine: ↓ imatinib intracellular exposure[9,18,64,65]	• ↓ **dasatinib absorption**[9] (↓ dasatinib solubility) • Inhibition of Pgp by ranitidine: ↑ dasatinib exposure[18,65]	—
Antiemetics			
Metoclopramide	—	• ↑ **QT interval**[19] (additive effect) → **monitor ECG**	• ↑ **QT interval**[19] (additive effect) → **monitor ECG**
Antidiabetic drugs			
Insulin	—	—	—
Metformin	• Inhibition of hOCT1 by metformin: ↓ imatinib intracellular exposure[9,18,64]	—	—
Glibenclamide	• Inhibition of CYP 3A4 and 2C9 by imatinib: ↑ glibenclamide exposure[9,18,19] • Inhibition of Pgp by glibenclamide: ↑ imatinib exposure[9,18,64]	• Inhibition of CYP 3A4 by dasatinib: ↑ glibenclamide exposure[9,18,19] • Inhibition of Pgp by glibenclamide: ↑ dasatinib exposure[9,18,64]	• Inhibition of CYP 3A4 and 2C9 by nilotinib: ↑ glibenclamide exposure[9,18,19]
Acarbose	—	—	—
Rosiglitazone	• Inhibition of CYP 2C9 by imatinib: ↑ rosiglitazone exposure[9,18,19]	—	• Inhibition of CYP 2C9 by nilotinib: ↑ rosiglitazone exposure[9,18,19]
Pioglitazone	• Inhibition of CYP 3A4 and 2C9 by imatinib: ↑ pioglitazone exposure[9,18,19]	• Inhibition of CYP 3A4 by dasatinib: ↑ pioglitazone exposure[9,18,19]	• Inhibition of CYP 3A4 and 2C9 by nilotinib: ↑ pioglitazone exposure[9,18,19]
Nateglinide	• Inhibition of CYP 3A4 and 2C9 by imatinib: ↑ nateglinide exposure[9,18,19]	• Inhibition of CYP 3A4 by dasatinib: ↑ nateglinide exposure[9,18,19]	• Inhibition of CYP 3A4 and 2C9 by nilotinib: ↑ nateglinide exposure[9,18,19]
Repaglinide	• Inhibition of CYP 3A4 by imatinib: ↑ repaglinide exposure[9,18,19]	• Inhibition of CYP 3A4 and 2C8 by dasatinib: ↑ repaglinide exposure[9,18,19]	• Inhibition of CYP 3A4 and 2C8 by nilotinib: ↑ repaglinide exposure[9,18,19]

P-450 Enzyme System," "P-Glycoprotein," "ABCG2 protein," "organic cation transporter 1," "Protein binding," and the respective TKI and concomitant drugs names. In addition, 2 drug information databases (UpToDate online[18] and Cancer Care Ontario[19]) were screened, and abstracts of international and national conferences, review articles, and references given in identified articles were also scanned.[20-22] All relevant cited literature on pharmacokinetic or pharmacodynamic interactions was considered for inclusion in Table 1.

Drug interactions were either clinically documented or derived from mechanistic considerations on proven or putative metabolic pathways, protein binding, and transmembrane transport. When data on a particular combination were unavailable, potential interactions were extrapolated from the reported disposition mechanisms of the agents and of similar substrates.

Interaction with imatinib

Imatinib is metabolized mainly by CYP isoenzyme 3A4, whereas CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A5 are reported to play a minor role in its metabolism.[11] This TKI has also been shown to be a substrate of hOCT1, Pgp, and BCRP.[9,23-25] However, a controversial report[26] suggests that imatinib is an inhibitor rather than a substrate of BCRP, thus leaving uncertainty about the role of this pathway. The metabolites of imatinib are eliminated predominantly through biliary excretion. One metabolite, an N-demethylated piperizine derivative (CGP 74588) shows pharmacologic activity comparable to the parent drug, but the

Part 2. Blood and blood-forming organs

	Imatinib	Dasatinib	Nilotinib
Antiplatelet drug*			
Clopidogrel	• Inhibition of CYP 3A4 and 2C19 by imatinib: ↑ clopidogrel exposure[9,18,19] ↓ clopidogrel bioactivation[9,18,19]	• Inhibition of CYP 3A4 by dasatinib: ↑ clopidogrel exposure[9,18,19] ↓ clopidogrel bioactivation[9,18,19] • **Thrombocytopenic effect of dasatinib:** ↑ **risk of bleeding**[9,18,19]	• Inhibition of CYP 3A4 by nilotinib: ↑ clopidogrel exposure[9,18,19] ↓ clopidogrel bioactivation[9,18,19]
Anticoagulants*			
Acenocoumarol	• **Inhibition of CYP 2C9 by imatinib:** ↑ **anticoagulation** → **monitor PT/INR**[9]	• **Thrombocytopenic effect of dasatinib:** ↑ **risk of bleeding**[9,18,19]	• **Inhibition of CYP 2C9 by nilotinib:** ↑ **anticoagulation** → **monitor PT/INR**[9]
Phenprocoumon	• **Inhibition of CYP 2C9 by imatinib:** ↑ **anticoagulation** → **monitor PT/INR**[9]	• **Thrombocytopenic effect of dasatinib:** ↑ **risk of bleeding**[9,18,19]	• **Inhibition of CYP 2C9 by nilotinib:** ↑ **anticoagulation** → **monitor PT/INR**[9]
Warfarin	• **Inhibition of CYP 2C9 by imatinib:** ↑ **anticoagulation** → **monitor PT/INR**[9]	• **Thrombocytopenic effect of dasatinib:** ↑ **risk of bleeding**[9,18,19]	• **Inhibition of CYP 2C9 by nilotinib:** ↑ **anticoagulation** → **monitor PT/INR**[9]
Heparin	• **Inhibition of Pgp by heparin:** ↑ **imatinib exposure**[66]	• **Thrombocytopenic effect of dasatinib:** ↑ **risk of bleeding**[9,18,19] • **Inhibition of Pgp by heparin:** ↑ **dasatinib exposure**[9,10,52,66-68]	—
Enoxaparin	—	• **Thrombocytopenic effect of dasatinib:** ↑ **risk of bleeding**[9,18,19]	—
Nadroparin	—	• **Thrombocytopenic effect of dasatinib:** ↑ **risk of bleeding**[9,18,19]	—
Dalteparin	—	• **Thrombocytopenic effect of dasatinib:** ↑ **risk of bleeding**[9,18,19]	—

*TKIs in general can cause thrombocytopenia, which is usually of no clinical relevance. Please take that into consideration when coadministrating with anticoagulant medication.

PT indicates prothrombin time; INR, international normalized ratio.

systemic exposure represents ~ 15% of that for imatinib.[13] The fecal-to-urinary excretion ratio is ~ 5:1. Moreover, imatinib can competitively inhibit the metabolism of drugs that are CYP2C9, CYP2C19, CYP2D6, and CYP3A4 substrates.[13] Imatinib is ~ 95% bound to human plasma proteins, mainly albumin and α1-acid glycoprotein.[11,27-29]

Interactions should therefore be considered when administering inhibitors of the CYP3A family in combination with imatinib. Strong inhibition, such as achieved with ketoconazole, caused a 40% increase of imatinib exposure in healthy volunteers.[30] Interactions are likely to occur with other inhibitors of CYP3A4, such as levothyroxine[31,32] voriconazole,[33] or amiodarone,[34] leading to an increase in plasma concentrations of imatinib. Nevertheless, a study suggests that inhibition of CYP3A4 by the potent irreversible inhibitor ritonavir does not result in increased steady-state plasma concentrations of imatinib, possibly because of the induction of compensatory metabolism or transport mechanisms by ritonavir.[35]

Concomitant administration of imatinib with inhibitors of both CYP3A4 and Pgp increase not only plasma but also intracellular imatinib concentrations. Dual CYP3A4 and Pgp inhibitors such as verapamil,[9] erythromycin,[36] clarithromycin,[36] ciclosporin,[37,38] ketoconazole,[30] fluconazole,[9,18] and itraconazole[9,18] increase intracellular concentrations of imatinib by inhibiting both its metabolism and its efflux by Pgp and might therefore increase its cellular toxicity.

Moreover, inhibition of Pgp by proton pump inhibitors such as pantoprazole was shown to increase brain penetration of imatinib.[40] Conversely, another study reported that concomitant administration of a Mg^{2+}-Al^{3+}–based antacid is not associated with meaningful alterations in imatinib absorption.[41]

Concomitant administration of CYP3A4 inducers such as rifampicin or certain antiepileptics may lead to a reduction of as much as 74% in imatinib exposure.[12,13,42] Moreover, the pharmacokinetic profile of imatinib was significantly altered by St John's wort, with reductions of 30% in the median area under the concentration-time curve (AUC).[43,44] Concomitant use of enzyme inducers, including St John's wort, may thus necessitate an increase in imatinib dosages to maintain clinical effectiveness.[43,44]

Interactions with quinidine, ranitidine, or midazolam, known inhibitors of hOCT1, may paradoxically increase the circulating concentrations of imatinib but decrease the intracellular exposure of target cancer cells, known to express this carrier.[9,25]

With regard to all these mechanisms, it is worth recalling that plasma concentrations of imatinib appear correlated with efficacy and toxicity.[29,45-47] A change in imatinib exposure because of a drug interaction might therefore definitely influence its therapeutic efficacy.

TKIs can also inhibit drug transporters and enzymes, leading to changes in the exposure of coadministered drugs. Imatinib enhances the intestinal absorption of ciclosporin, a CYP3A4 and Pgp substrate, and may increase the pharmacologic effects and possibly toxicity of ciclosporin.[37,38] Moreover, the clearance of simvastatin (a CYP3A4 substrate) was reduced by 70% when associated with imatinib.[13] Administration of imatinib together with metoprolol, a CYP2D6 substrate, resulted in an increase in metoprolol exposure by 23%.[13]

Data concerning interactions involving protein binding are poorly documented for imatinib. A study showed that St John's wort does not alter the protein binding of imatinib over a wide range of concentrations in vivo.[43,44]

Interactions of potential clinical relevance can occur with calcium channel blockers such as verapamil and diltiazem, substrates of CYP3A4, which circulating levels are increased

Part 3. Cardiovascular system

	Imatinib	Dasatinib	Nilotinib
Calcium channel blockers			
Verapamil	• Inhibition of CYP 3A4 and Pgp by imatinib: ↑ verapamil exposure[9,23,24,55,69-72] • **Inhibition of CYP 3A4 and Pgp by verapamil: ↑ imatinib exposure**[24,69,70,72]	• Inhibition of CYP 3A4 by dasatinib: ↑ verapamil exposure[9,18] • **Inhibition of CYP 3A4 and Pgp by verapamil: ↑ dasatinib exposure**[9,10,52,67,68]	• Inhibition of CYP 3A4 and Pgp by nilotinib: ↑ verapamil exposure[9,18,19,25,73] • Inhibition of CYP 3A4 by verapamil: ↑ nilotinib exposure[9,18,19]
Diltiazem	• **Inhibition of CYP 3A4 by imatinib: ↑ diltiazem exposure**[9,18] • Inhibition of CYP 3A4 and Pgp by diltiazem: ↑ imatinib exposure[9,23,24,55,69-72]	• Inhibition of CYP 3A4 by dasatinib: ↑ diltiazem exposure[9,18] • **Inhibition of CYP 3A4 and Pgp by diltiazem: ↑ dasatinib exposure**[9,10,52,67,68]	• Inhibition of CYP 3A4 by nilotinib: ↑ diltiazem exposure[9,18] • Inhibition of CYP 3A4 by diltiazem: ↑ nilotinib exposure[9,18,19]
Nifedipine	• **Inhibition of CYP 3A4 by imatinib: ↑ nifedipine exposure**[9,18,74]	• **Inhibition of CYP 3A4 by dasatinib: ↑ nifedipine exposure**[9,18,74]	• Inhibition of CYP3A4 by nilotinib: ↑ nifedipine exposure[9,18,74]
Amlodipine	• **Inhibition of CYP 3A4 by imatinib: ↑ amlodipine exposure**[9,18,19]	• **Inhibition of CYP 3A4 by dasatinib: ↑ amlodipine exposure**[9,18,19]	• Inhibition of CYP 3A4 by nilotinib: ↑ amlodipine exposure[9,18,19]
NO precursors			
Molsidomine	—	—	—
Isosorbid mononitrate (ISMN)	• Inhibition of CYP 3A4 by imatinib: ↑ ISMN exposure[9,18,19]	• Inhibition of CYP 3A4 by dasatinib: ↑ ISMN exposure[9,18,19]	• Inhibition of CYP 3A4 by nilotinib: ↑ ISMN exposure[9,18,19]
Isosorbid dinitrate (ISDN)	• Inhibition of CYP 3A4 by imatinib: ↑ ISDN exposure[9,18,19]	• Inhibition of CYP 3A4 by dasatinib: ↑ ISDN exposure[9,18,19]	• Inhibition of CYP 3A4 by nilotinib: ↑ ISDN exposure[9,18,19]
Nitroglycerine	—	—	—
HMG-CoA reductase inhibitors			
Simvastatin	• **Inhibition of CYP 3A4 by imatinib: ↑ simvastatin exposure**[9,18,19,48] • **Inhibition of Pgp by simvastatin: ↑ imatinib exposure**[9,23,24,55,69-72]	• **Inhibition of CYP 3A4 by dasatinib: ↑ simvastatin exposure**[9,18,19,48] • Inhibition of Pgp by simvastatin: ↑ dasatinib exposure[9,10,52,67,68]	• Inhibition of CYP 3A4 by nilotinib: ↑ simvastatin exposure[9,18,19]
Pravastatin	—	—	—
Atorvastatin	• **Inhibition of CYP 3A4 by imatinib: ↑ atorvastatin exposure**[9,18,19] • Inhibition of Pgp by atorvastatin: ↑ imatinib exposure[9,23,24,55,69-72]	• Inhibition of CYP 3A4 by dasatinib: ↑ atorvastatin exposure[9,18,19] • Inhibition of Pgp by atorvastatin: ↑ dasatinib exposure[9,10,67,68]	• Inhibition of CYP 3A4 by nilotinib: ↑ atorvastatin exposure[9,18,19]
Rosuvastatin	—	—	—
Antiarrhythmic drugs			
Amiodarone	• Inhibition of CYP 3A4 and Pgp by imatinib: ↑ amiodarone exposure[9,23,24,69,70,72,75] • Inhibition of CYP3A4 and Pgp by amiodarone: ↑ imatinib exposure[9,23,24,69,70,72,75] • Inhibition of hOCT1 by amiodarone: ↓ imatinib intracellular exposure[9,18,64]	• Inhibition of CYP 3A4 by dasatinib: ↑ amiodarone exposure[9,23,24,69,70,72,75] • Inhibition of CYP 3A4 and Pgp by amiodarone: ↑ dasatinib exposure[9,10,67,68,75] • ↑ **QT interval**[19] (additive effect) → **monitor ECG**	• Inhibition of Pgp and CYP 3A4 by nilotinib: ↑ amiodarone exposure[9,18,19,25,73] • Inhibition of CYP 3A4 by amiodarone: ↑ nilotinib exposure[9,18,19] • ↑ **QT interval**[19] (additive effect) → **monitor ECG**
Quinidine	• **Inhibition of CYP 3A4 by imatinib: ↑ quinidine exposure**[9,18,19] • Inhibition of Pgp by quinidine: ↑ imatinib exposure[9,23,24,55,69-72] • Inhibition of hOCT1 by quinidine: ↓ imatinib intracellular exposure[9,18,65]	• **Inhibition of CYP 3A4 by dasatinib: ↑ quinidine exposure**[9,18,19] • Inhibition of Pgp by quinidine: ↑ dasatinib exposure[9,18,19] • ↑ **QT interval**[19] (additive effect) → **monitor ECG**	• Inhibition of CYP 3A4 by nilotinib: ↑ quinidine exposure[9,18,19] • ↑ **QT interval**[19] (additive effect) → **monitor ECG**
Diuretics			
Furosemide	• **Absence of interaction**[76]	—	—
Torasemide	• Inhibition of CYP 2C9 by imatinib: ↑ torasemide exposure[9,18]	—	• Inhibition of CYP 2C9 by nilotinib: ↑ torasemide exposure[9,18]
Hydrochlorothiazide	—	—	—
Spironolactone	• Inhibition of Pgp by spironolactone: ↑ imatinib exposure[9,64]	• Inhibition of Pgp by spironolactone: ↑ dasatinib exposure[9,10,52,64,67]	—
Beta blockers			
Metoprolol	• **Inhibition of CYP 2D6 by imatinib: ↑ metoprolol exposure**[18]	• Inhibition of Pgp by metoprolol: ↑ dasatinib exposure[9,10,52,67]	• Inhibition of CYP 2D6 by nilotinib: ↑ metoprolol exposure[9,18,19]
Bisoprolol	• **Inhibition of CYP 2D6 by imatinib: ↑ bisoprolol exposure**[18]	• Inhibition of CYP 3A4 by dasatinib: ↑ bisoprolol exposure[9,18]	• Inhibition of CYP 2D6 by nilotinib: ↑ bisoprolol exposure[9,18,19]
Carvedilol	• Inhibition of CYP 2C9 and 2D6 by imatinib: ↑ carvedilol exposure[18] • Inhibition of Pgp by carvedilol: ↑ imatinib exposure[64,71,77]	• Inhibition of Pgp by carvedilol: ↑ dasatinib exposure[9,10,52,67,68,77]	• Inhibition of CYP 2C9 and 2D6 by nilotinib: ↑ carvedilol exposure[9,18,19]
Atenolol	• **Absence of interaction**[9]	—	—
ACE inhibitors			
Captopril	• Inhibition of CYP 2D6 by imatinib: ↑ captopril exposure[18] • Inhibition of Pgp by captopril: ↑ imatinib exposure[9,18,23,64,70,72]	• Inhibition of Pgp by captopril: ↑ dasatinib exposure[9,10,52,67]	• Inhibition of CYP 2D6 by nilotinib: ↑ captopril exposure[9,18,19]
Enalapril	• Inhibition of CYP 3A4 by imatinib: ↑ enalapril exposure[18] • Inhibition of Pgp by enalapril: ↑ imatinib exposure[9,18,23,64,70,72]	• Inhibition of Pgp by enalapril: ↑ dasatinib exposure[9,10,52,67]	• Inhibition of CYP 3A4 by nilotinib: ↑ enalapril exposure[9,18,19]
Ramipril	—	—	—

Part 3. Cardiovascular system (continued)

	Imatinib	Dasatinib	Nilotinib
Lisinopril	• Inhibition of Pgp by imatinib: ↑ lisinopril exposure[9,18,23,64,70,72] • Inhibition of Pgp by lisinopril: ↑ imatinib exposure[9]	• Inhibition of Pgp by lisinopril: ↑ dasatinib exposure[9,10,52,67]	—
AT II receptor blockers			
Losartan	• Inhibition of CYP 2C9 and 3A4 by imatinib: losartan exposure and ↓ losartan bioactivation[9,18,19] • Inhibition of Pgp by losartan: ↑ imatinib exposure[9,18,19]	• Inhibition of CYP 3A4 by dasatinib: ↑ losartan exposure[9,18] • Inhibition of Pgp by losartan: ↑ dasatinib exposure[9,10,52,67]	• Inhibition of CYP 2C9 and 3A4 by nilotinib: ↑ losartan exposure and ↓ losartan bioactivation[9,18,19]
Candesartan	—	—	—
Cardiac glycosides			
Digoxin	• ↓ **digoxin absorption**[9,18,19] (unknown mechanism)	• ↑ **QT interval**[19] (additive effect) → **monitor ECG**	• ↑ **QT interval**[19] (additive effect) → **monitor ECG** • Inhibition of Pgp by nilotinib: ↑ digoxin exposure[9,18,19]

when associated with imatinib.[18,19] Interactions with simvastatin, amiodarone, and quinidine, involving the same P450 isoenzyme, may also be of clinical relevance.[9,18,19,48] In patients taking imatinib, such drugs should be either tapered or avoided and replaced by safer alternatives (eg, pravastatin or sotalol).

Imatinib is also known to inhibit the O-glucuronidation of acetaminophen, possibly inducing hepatotoxicity and liver failure.[9] The use of acetaminophen should be limited in patients taking imatinib. A limit has been suggested of 1300 mg acetaminophen per day.[49] Liver function tests might be useful to monitor during prolonged treatment.[50] Acenocoumarol and phenprocoumon, substrates of CYP2C9, show also increased concentrations; however, this interaction can be compensated by the monitoring of prothrombin time or international normalized ratio.[9,18,51]

Finally, physicians should be aware that patients with hypothyroid conditions who receive imatinib need increased levothyroxine doses.[31,32] The suspected mechanism responsible for this phenomenon is an induction of non–deiodination clearance.[31,32] The fraction of levothyroxine that is deiodinated into biologically active triiodothyronine is mainly subject to conjugation with glucuronates and sulfates.[31,32] Although the liver primarily mediates glucuronidation and sulfation, these conjugations occur in extrahepatic sites such as the kidney and intestine as well.[31,32] Therefore, induction of uridine diphosphate–glucuronyl transferases (UGTs) seems to be involved.[31,32] A 2-fold increase in levothyroxine substitution therapy at initiation of imatinib treatment is recommended, along with close monitoring of thyroid function.[31,32]

Interaction with dasatinib

Dasatinib is metabolized in an active derivative and other inactive metabolites by the CYP3A4 isoenzyme and was also reported to be a substrate of BCRP and Pgp.[9,18,52] The active metabolite appears to play a negligible role in therapeutic activity. Dasatinib has an inhibitory activity against CYP2C8 and CYP3A4. Plasma protein binding is ~ 96% for dasatinib, mainly to albumin.[53,54]

Part 4. Hormonal preparations

	Imatinib	Dasatinib	Nilotinib
Corticosteroids			
Prednisone	—	—	—
Dexamethasone	• **Induction of CYP 3A4 by dexamethasone:** ↓ **imatinib exposure**[19]	• **Induction of CYP 3A4 by dexamethasone:** ↓ **dasatinib exposure**[19]	• Induction of CYP 3A4 by dexamethasone: ↓ nilotinib exposure[9,18,19]
Betamethasone	—	—	—
Thyroid therapy			
Levothyroxine	• **Induction of UGTs by imatinib:** ↓ **levothyroxine**[31,32] • **Inhibition of CYP 3A4 by levothyroxine:** ↑ **imatinib exposure**[31,32]	• Inhibition of CYP 3A4 by levothyroxine: ↑ dasatinib exposure[9,19]	• Inhibition of CYP 3A4 by levothyroxine: ↑ nilotinib exposure[9,19]
Carbimazole	—	—	—
Antineoplastic agents			
Cyclophosphamide	• Inhibition of CYP 2D6 and 3A4 by imatinib: ↑ cyclophosphamide exposure ↓ cyclophosphamide bioactivation[9,19]	• Inhibition of CYP 3A4 by dasatinib: ↑ cyclophosphamide exposure ↓ cyclophosphamide bioactivation[9,19]	• **Induction of CYP 2B6 by nilotinib:** ↓ **cyclophosphamide exposure** ↑ **cyclophosphamide bioactivation**[19] • Inhibition of CYP 3A4 and 2D6 by nilotinib: ↑ cyclophosphamide exposure[9,19] ↓ cyclophosphamide bioactivation[19]
Antiestrogen agent			
Tamoxifen	• **Inhibition of CYP 2D6 and 3A4 by imatinib:** ↑ **tamoxifen exposure** ↓ **tamoxifen bioactivation**[18,78]	• Inhibition of CYP 3A4 by dasatinib: ↑ tamoxifen exposure ↓ tamoxifen bioactivation[18,78]	• **Inhibition of CYP 2D6 and 3A4 by nilotinib:** ↑ **tamoxifen exposure** ↓ **tamoxifen bioactivation**[18,78]

Part 5. Anti-infectives

	Imatinib	Dasatinib	Nilotinib
Penicillins			
Amoxicillin	—	—	—
Flucloxacillin	—	—	—
Cephalosporins			
Céfuroxime	—	—	—
Cefpodoxime	—	—	—
Ceftriaxone	—	—	—
Macrolides			
Clarithromycin	• **Inhibition of CYP 3A4 and Pgp by clarithromycin:** ↑ **imatinib exposure**[9,18,19,36]	• **Inhibition of CYP 3A4 and Pgp by clarithromycin:** ↑ **dasatinib exposure**[9,18,19]	• **Inhibition of CYP 3A4 by clarithromycin:** ↑ **nilotinib exposure**[9,18,19]
Azithromycin	—	—	—
Erythromycin	• **Inhibition of CYP 3A4 and Pgp by erythromycin:** ↑ **imatinib exposure**[9,18,19,36]	• **Inhibition of CYP 3A4 and Pgp by erythromycin:** ↑ **dasatinib exposure**[9,18,19]	• Inhibition of CYP 3A4 by erythromycin: ↑ nilotinib exposure[9,18,19]
Tetracyclines			
Doxycyclin	—	—	—
Quinolones			
Ciprofloxacin	• Inhibition of Pgp by ciprofloxacin: ↑ imatinib exposure[9,18,23,64,70,72]	• ↑ **QT interval**[18,19] (additive effect) → **monitor ECG** • Inhibition of Pgp by ciprofloxacin: ↑ dasatinib exposure[9,10,52,67,68]	• ↑ **QT interval**[18,19] (additive effect) → **monitor ECG**
Levofloxacin	• Inhibition of Pgp by levofloxacin: ↑ imatinib exposure[9,18,23,64,70,72] • Inhibition of hOCT1 by levofloxacine: ↓ imatinib intracellular exposure[9,18,64]	• ↑ **QT interval**[18,19] (additive effect) → **monitor ECG** • Inhibition of Pgp by levofloxacin: ↑ dasatinib exposure[9,10,52,67,68]	• ↑ **QT interval**[18,19] (additive effect) → **monitor ECG**
Norfloxacin	—	• ↑ **QT interval**[18,19] (additive effect) → **monitor ECG**	• ↑ **QT interval**[18,19] (additive effect) → **monitor ECG**
Sulfonamides			
Co-trimoxazole	• Inhibition of CYP 2C9 by imatinib: ↑ co-trimoxazole[9,18,19]	—	• Inhibition of CYP 2C9 by nilotinib: ↑ co-trimoxazole[9,18,19]
Azoles			
Itraconazole	• **Inhibition of CYP 3A4 and Pgp by itraconazole:** ↑ **imatinib exposure**[9,18,19]	• **Inhibition of CYP 3A4 and Pgp by itraconazole:** ↑ **dasatinib exposure**[9,18,19]	• **Inhibition of CYP 3A4 by itraconazole:** ↑ **nilotinib exposure**[9,18,19]
Fluconazole	• **Inhibition of CYP 3A4 and Pgp by fluconazole:** ↑ **imatinib exposure**[9,18,19]	• Inhibition of CYP 3A4 and Pgp by fluconazole: ↑ dasatinib exposure[9,18,19] • ↑ **QT interval**[18,19] (additive effect) → **monitor ECG**	• Inhibition of CYP 3A4 by fluconazole: ↑ nilotinib exposure[9,18,19] • ↑ **QT interval**[18,19] (additive effect) → **monitor ECG**
Voriconazole	• **Inhibition of CYP 3A4 by voriconazole:** ↑ **imatinib exposure**[9,18,19,33]	• Inhibition of CYP 3A4 by voriconazole: ↑ dasatinib exposure[9,18,19] • ↑ **QT interval** (additive effect) → **monitor ECG**	• Inhibition of CYP 3A4 by voriconazole: ↑ nilotinib exposure[9,18,19] • ↑ **QT interval**[18,19] (additive effect) → **monitor ECG**
Ketoconazole	• **Inhibition of CYP 3A4 and Pgp by ketoconazole:** ↑ **imatinib exposure**[9,18,19,30]	• **Inhibition of CYP 3A4 and Pgp by ketoconazole:** ↑ **dasatinib exposure**[9,18,19] • ↑ **QT interval**[18,19] (additive effect) → **monitor ECG**	• Inhibition of CYP 3A4 by ketoconazole: ↑ nilotinib exposure[9,18,19] • ↑ **QT interval**[18,19] (additive effect) → **monitor ECG**
Allylamine			
Terbinafine	• Inhibition of CYP 3A4 and 2C9 by imatinib: ↑ terbinafine exposure[9,18,19]	• Inhibition of CYP 3A4 by dasatinib: ↑ terbinafine exposure[9,18,19]	• Inhibition of CYP 3A4 and 2C9 by nilotinib: ↑ terbinafine exposure[9,18,19]
Nitroimidazole			
Metronidazole	—	—	—
Antiviral/nucleoside analog			
Aciclovir	• **Absence of interaction**[79]	—	—
Valaciclovir	• **Absence of interaction**[79]	—	—
Ganciclovir	• Inhibition of hOCT1 by ganciclovir: ↓ imatinib intracellular exposure[9,18,19]	—	—
Valganciclovir	• Inhibition of hOCT1 by ganciclovir: ↓ imatinib intracellular exposure[9,18,19]	—	—
Antimycobacterials			
Rifampicine	• **Induction of CYP 3A4 by rifampicine:** ↓ **imatinib exposure**[9,18,80]	• **Induction of CYP 3A4 by rifampicine:** ↓ **dasatinib exposure**[9,18,19]	• **Induction of CYP 3A4 by rifampicine:** ↓ **nilotinib exposure**[9,18,19]
Isoniazide	—	—	—
Ethambutol	—	—	—

Part 5. Anti-infectives (continued)

	Imatinib	Dasatinib	Nilotinib
Protease inhibitors			
Ritonavir	• Inhibition of CYP 3A4 and Pgp by ritonavir: ↑ imatinib exposure[9,18,19,81]	• **Inhibition of CYP 3A4 and Pgp by ritonavir:** ↑ **dasatinib exposure**[9,18,19,81] • ↑ **QT interval**[18,19] (additive effect) → **monitor ECG**	• Inhibition of CYP 3A4 by ritonavir: ↑ nilotinib exposure[9,18,19,81] • ↑ **QT interval**[18,19] (additive effect) → **monitor ECG**
Saquinavir	• Inhibition of CYP 3A4 and Pgp by imatinib: ↑ saquinavir exposure[9,18,19,81] • Inhibition of hOCT1 by saquinavir: ↓ imatinib intracellular exposure[9,18,64]	• Inhibition of CYP 3A4 by dasatinib: ↑ saquinavir exposure[9,18,19,81]	• Inhibition of CYP 3A4 and Pgp by nilotinib: ↑ saquinavir exposure[9,18,19,81]
Darunavir	• Inhibition of CYP 3A4 by darunavir: ↑ imatinib exposure[9,18,19,81]	• Inhibition of CYP 3A4 by darunavir: ↑ dasatinib exposure[9,18,19,81]	• Inhibition of CYP 3A4 by darunavir: ↑ nilotinib exposure[9,18,19,81]
Atazanavir	• Inhibition of CYP 3A4 and Pgp by imatinib: ↑ atazanavir exposure[9,18,19,81]	• Inhibition of CYP 3A4 by dasatinib: ↑ atazanavir exposure[9,18,19,81]	• Inhibition of CYP 3A4 and Pgp by nilotinib: ↑ atazanavir exposure[9,18,19,81]
Lopinavir	• Inhibition of CYP 3A4 and Pgp by imatinib: ↑ lopinavir exposure[9,18,19,81] • Inhibition of CYP 3A4 and Pgp by lopinavir/ritonavir*: ↑ imatinib exposure[9,18,19,81]	• Inhibition of CYP 3A4 by dasatinib: ↑ lopinavir exposure[9,18,19,81] • Inhibition of CYP 3A4 and Pgp by lopinavir/ritonavir*: ↑ dasatinib exposure[9.18.19.81]	• Inhibition of CYP 3A4 and Pgp by nilotinib: ↑ lopinavir exposure[9,18,19,81] • Inhibition of CYP 3A4 by lopinavir/ritonavir*: ↑ nilotinib exposure[9,18,19,81]
Indinavir	• Inhibition of CYP 3A4 and Pgp by imatinib: ↑ indinavir exposure[9,18,19,81] • Inhibition of hOCT1 by indinavir: ↓ imatinib intracellular exposure[9,18,64]	• Inhibition of CYP 3A4 by dasatinib: ↑ indinavir exposure[9,18,19,81]	• Inhibition of CYP 3A4 and Pgp by nilotinib: ↑ indinavir exposure[9,18,19,81]
Nucleoside and nucleotide reverse transcriptase inhibitors			
Lamivudine	• Inhibition of hOCT1 by lamivudine: ↓ imatinib intracellular exposure[9,18,64]	—	—
Emtricitabine	—	—	—
Zidovudine	—	—	—
Non-nucleoside reverse transcriptase inhibitors			
Efavirenz	• Inhibition of CYP 3A4 by imatinib: ↑ efavirenz exposure[9,18,19,81] • Induction of CYP 3A4 by efavirenz: ↓ imatinib exposure[9,18,19,81]	• Inhibition of CYP 3A4 by dasatinib: ↑ efavirenz exposure[9,18,19,81] • Induction of CYP 3A4 by efavirenz: ↓ dasatinib exposure[9,18,19,81]	• Inhibition of CYP 3A4 by nilotinib: ↑ efavirenz exposure[9,18,19,81] • Induction of CYP 3A4 by efavirenz: ↓ nilotinib exposure[9,18,19,81]
Nevirapine	• Inhibition of CYP 3A4 by imatinib: ↑ nevirapine exposure[9,18,19,81] • Induction of CYP 3A4 by nevirapine: ↓ imatinib exposure[9,18,19,81]	• Inhibition of CYP 3A4 by dasatinib: ↑ nevirapine exposure[9,18,19,81] • Induction of CYP 3A4 by nevirapine: ↓ dasatinib exposure[9,18,19,81]	• Inhibition of CYP 3A4 by nilotinib: ↑ nevirapine exposure[9,18,19,81] • Induction of CYP 3A4 by nevirapine: ↓ nilotinib exposure[9,18,19,81]
Etravirine	• Inhibition of CYP 2C9 and 3A4 by imatinib: ↑ etravirine exposure[9,18,19,81] • Induction of CYP 3A4 by etravirine: ↓ imatinib exposure[9,18,19,81]	• Inhibition of CYP 3A4 by dasatinib: ↑ etravirine exposure[9,18,19,81] • Induction of CYP 3A4 by etravirine: ↓ dasatinib exposure[9,18,19,81]	• Inhibition of CYP 2C9 and 3A4 by nilotinib: ↑ etravirine exposure[9,18,19,81] • Induction of CYP 3A4 by etravirine: ↓ nilotinib exposure[9,18,19,81]
Antimalarial drugs			
Quinine	• Inhibition of CYP 3A4 by imatinib: ↑ quinine exposure[9,18,19] • **Inhibition of CYP 2D6 and Pgp by quinine:** ↑ **imatinib exposure**[9,18,19] • Inhibition of hOCT1 by quinine: ↓ imatinib intracellular exposure[9,18,64]	• Inhibition of CYP 3A4 by dasatinib: ↑ quinine exposure[9,18,19] • **Inhibition of CYP 3A4 by dasatinib:** ↑ **quinine exposure**[9,18,19] • ↑ **QT interval**[18,19] (additive effect) → **monitor ECG**	• Inhibition of CYP 3A4 by nilotinib: ↑ quinine exposure[9,18,19] • ↑ **QT interval**[18,19] (additive effect) → **monitor ECG**
Chloroquine	• Inhibition of Pgp by chloroquine: ↑ imatinib exposure[9,18,19] • Inhibition of hOCT1 by chloroquine: ↓ imatinib intracellular exposure[9,18,64]	• Inhibition of Pgp by chloroquine: ↑ dasatinib exposure[9,18,19] • ↑ **QT interval**[18,19] (additive effect) → **monitor ECG**	• ↑ **QT interval**[18,19] (additive effect) → **monitor ECG**
Mefloquine	• Inhibition of CYP 3A4 and Pgp by imatinib: ↑ mefloquine exposure[9,18,19] • Inhibition of Pgp by mefloquine: ↑ imatinib exposure[9,18,19]	• Inhibition of CYP 3A4 by dasatinib: ↑ mefloquine exposure[9,18,19] • Inhibition of Pgp by mefloquine: ↑ dasatinib exposure[9,18,19] • ↑ **QT interval**[18,19] (additive effect) → **monitor ECG**	• Inhibition of CYP 3A4 and Ppg by nilotinib: ↑ mefloquine exposure[9,18,19] • ↑ **QT interval**[18,19] (additive effect) → **monitor ECG**
Proguanil	• Inhibition of CYP 2C19 and Pgp by imatinib: ↑ proguanil exposure ↓ proguanil bioactivation[9,18,19]	—	—
Atovaquone	—	—	—
Doxycycline	—	—	—

*As lopinavir is co-administered with ritonavir, the net clinical effect observed is inhibition of CYP 3A4 and Pgp by ritonavir, and therefore increase of TKI exposure.

Part 6. Immunomodulating agents

	Imatinib	Dasatinib	Nilotinib
Immunosuppressants			
Ciclosporin	• **Inhibition of CYP 3A4 and Pgp by imatinib:** ↑ **ciclosporin exposure**[37,38] • **Inhibition of Pgp and CYP 3A4 by ciclosporin:** ↑ **imatinib exposure**[37,38]	• Inhibition of CYP 3A4 by dasatinib: ↑ ciclosporin exposure[9,18,19,82] • Inhibition of CYP3A4 and Pgp by ciclosporin: ↑ dasatinib exposure[9,18,19,82]	• Inhibition of CYP 3A4 and Pgp by nilotinib: ↑ ciclosporin exposure[9,18,19,82] • Inhibition of CYP3A4 by ciclosporin: ↑ nilotinib exposure[9,18,19,82]
Tacrolimus	• Inhibition of CYP 3A4 by imatinib: ↑ tacrolimus exposure[9,18,19,82] • Inhibition of Pgp by tacrolimus: ↑ imatinib exposure[9,18,19,82]	• Inhibition of CYP 3A4 by dasatinib: ↑ tacrolimus exposure[9,18,19,82] • Inhibition of Pgp by tacrolimus: ↑ dasatinib exposure[9,18,19,82]	• Inhibition of CYP 3A4 and Pgp by nilotinib: ↑ tacrolimus exposure[9,18,19,82]
Sirolimus	• Inhibition of CYP 3A4 and Pgp by imatinib: ↑ sirolimus exposure[9,18,19,82]	• Inhibition of CYP 3A4 by dasatinib: ↑ sirolimus exposure[9,18,19,82]	• Inhibition of CYP 3A4 and Pgp by nilotinib: ↑ sirolimus exposure[9,18,19,82]
Everolimus	• Inhibition of CYP 3A4 and Pgp by imatinib: ↑ everolimus exposure[9,18,19,82]	• Inhibition of CYP 3A4 by dasatinib: ↑ everolimus exposure[9,18,19,82]	• Inhibition of CYP 3A4 and Pgp by nilotinib: ↑ everolimus exposure[9,18,19,82]
Mycophenolate mofetil	—	—	—
Methotrexate	—	—	—
Azathioprine	—	—	—

In healthy subjects receiving ketoconazole, systemic exposure (AUC) to dasatinib was increased by 5-fold.[39] Interactions may then occur between dasatinib and other inhibitors of CYP3A4, such as levothyroxine[31,32] and voriconazole,[33] leading to a marked increase in plasma concentrations of this TKI. Drugs that inhibit both BCRP and CYP3A4, such as verapamil,[55] may lead to even larger increase in dasatinib exposure.

Inhibitors of both CYP3A4 and Pgp will increase not only plasma but also intracellular concentrations of dasatinib; this is expected for verapamil,[9] erythromycin,[9,18] clarithromycin,[9,18] ciclosporin,[38] ketoconazole,[39] fluconazole,[9,18] and itraconazole.[9,18]

Concomitant administration of the CYP3A4 inducer rifampicin leads to a reduction of 80% in dasatinib exposure.[12,13,42] St John's wort, a CYP3A4 inducer, may also decrease dasatinib plasma concentrations and should be discouraged in patients receiving dasatinib.[56] Antiepileptics (phenobarbital, phenytoin, carbamazepine) are expected to decrease dasatinib concentrations as well.

Moreover, the solubility of dasatinib appears to be pH dependent. Dasatinib exposure is reduced by 61% when famotidine is administered before dasatinib dosing.[57] As a result, concomitant administration of agents that provide prolonged gastric acid suppression, such as H2 antagonists and proton pump inhibitors, is not recommended.[42] In contrast, dasatinib exposure is unchanged when Mg^{2+}-Al^{3+}–based antacids are administered $\geq$ 2 hours before dasatinib; but coadministration reduced dasatinib exposure by 55%-58%.[57]

Dasatinib can also slightly inhibit drug transporters and enzymes, leading to changes in the exposure of coadministered drugs.[9,18] The coingestion of dasatinib with simvastatin resulted in a 20% increased exposure to simvastatin.[13] Concurrent use with calcium channel blockers such as verapamil and diltiazem, substrates of CYP3A4, should be avoided.[18,51]

Studies about interactions involving protein binding were unavailable for dasatinib.

In clinical trials, dasatinib treatment has been associated with prolongation of the QTc interval on electrocardiograms, and sudden cardiac deaths have occurred, which are probably related to ventricular repolarization abnormalities.[58,59] Association of QT-prolonging drugs such as digoxin, quinolones, methadone, or several psychotropic medications, may increase the risk of such events by additive effect.[9,19] Regular electrocardiographic controls (ECG) are strongly recommended in such situations.[58,59]

Interactions with nilotinib

Nilotinib undergoes metabolism by CYP3A4. It is also a substrate of the efflux transporter BCRP.[9,23] Nilotinib is known to inhibit CYP2C8, CYP2C9, CYP2D6, CYP3A4, UGT1A1, and Pgp. In vitro studies suggest that nilotinib also induces CYP2B6 enzymes.[19] Note that UGT1A1 inhibition has been associated with an increase in bilirubin levels (especially in

Part 7. Musculoskeletal system

	Imatinib	Dasatinib	Nilotinib
NSAIDs			
Aspirin	—	• **Thrombocytopenic effect of dasatinib:** ↑ **risk of bleeding**[9,18,19]	—
Ibuprofen	• Inhibition of CYP 2C9 by imatinib: ↑ ibuprofen exposure[9,18,83,84]	• Inhibition of CYP 2C8 by dasatinib: ↑ ibuprofen exposure[9,18,83,84]	• Inhibition of CYP 2C8 and 2C9 by nilotinib: ↑ ibuprofen exposure[9,18,83,84]
Mefenacid	• Inhibition of CYP 2C9 by imatinib: ↑ mefenacid exposure[9,18,19]	• Inhibition of CYP 2C8 by dasatinib: ↑ mefenacid exposure[9,18,19]	• Inhibition of CYP 2C8 and 2C9 by nilotinib: ↑ mefenacid exposure[9,18,19]
Metamizole	• Induction of CYP 3A4 by metamizole: ↓ imatinib exposure[9,18,85]	• Induction of CYP 3A4 by metamizole: ↓ dasatinib exposure[9,18,85]	• Induction of CYP 3A4 by metamizole: ↓ nilotinib exposure[9,18,85]
Diclofenac	• Inhibition of CYP 2C9 by imatinib: ↑ diclofenac exposure[9,18,86] • Inhibition of Pgp by diclofenac: ↑ imatinib exposure[9,18,86]	• Inhibition of CYP 2C8 by dasatinib: ↑ diclofenac exposure[9,18,86] • Inhibition of Pgp by diclofenac: ↑ dasatinib exposure[9,18,86]	• Inhibition of CYP 2C8 and 2C9 by nilotinib: ↑ diclofenac exposure[9,18,86]
Antigout preparations			
Allopurinol	—	—	—

Part 8. Nervous system

	Imatinib	Dasatinib	Nilotinib
SSRI			
Fluoxetine	• Inhibition of CYP 2D6 by imatinib: ↑ fluoxetine exposure[9,18,19,87,88]	• ↑ **QT interval**[9,18,19,87,88] (additive effect) → **monitor ECG**	• ↑ **QT interval**[9,18,19,87,88] (additive effect) → **monitor ECG**
Fluvoxamine	• Inhibition of CYP 2D6 by imatinib: ↑ fluvoxamine exposure[9,18,19]	—	• Inhibition of CYP 2D6 by nilotinib: ↑ fluvoxamine exposure[9,18,19]
Paroxetine	• Inhibition of CYP 2D6 by imatinib: ↑ paroxetine exposure[9,18,19]	—	• Inhibition of CYP 2D6 by nilotinib: ↑ paroxetine exposure[9,18,19]
Citalopram	• Inhibition of CYP 3A4 and 2D6 by imatinib: ↑ citalopram exposure[9,18,19]	• Inhibition of CYP 3A4 by dasatinib: ↑ citalopram exposure[9,18,19]	• Inhibition of CYP 3A4 and 2D6 by nilotinib: ↑ citalopram exposure[9,18,19]
Sertraline	• Inhibition of CYP 3A4 and 2D6 by imatinib: ↑ sertraline exposure[9,18,19,87]	• Inhibition of CYP 3A4 by dasatinib: ↑ sertraline exposure[9,18,19,87]	• Inhibition of CYP 3A4 and 2D6 by nilotinib: ↑ sertraline exposure[9,18,19,87]
SSNRI			
Venlafaxine	• Inhibition of CYP 3A4 and 2D6 by imatinib: ↑ venlafaxine exposure[9,18,19,87]	• Inhibition of CYP 3A4 by dasatinib: ↑ venlafaxine exposure[9,18,19,87] • ↑ **QT interval**[18,19] (additive effect) → **monitor ECG**	• Inhibition of CYP 3A4 and 2D6 by nilotinib: ↑ venlafaxine exposure[9,18,19,87] • ↑ **QT interval**[18,19] (additive effect) → **monitor ECG**
Duloxetine	• Inhibition of CYP 2D6 by imatinib: ↑ duloxetine exposure[9,18,19]	—	• Inhibition of CYP 2D6 by nilotinib: ↑ duloxetine exposure[9,18,19]
Tetracyclic agent			
Mirtazapine	• Inhibition of CYP 3A4 and 2D6 by imatinib: ↑ mirtazapine exposure[9,18,19]	• Inhibition of CYP 3A4 by dasatinib: ↑ mirtazapine exposure[9,18,19]	• Inhibition of CYP 3A4 and 2D6 by nilotinib: ↑ mirtazapine exposure[9,18,19]
Tricyclic agents			
Trimipramine	• Inhibition of CYP 2D6 by imatinib: ↑ trimipramine exposure[9,18,19]	• ↑ **QT interval**[18,19] (additive effect) → **monitor ECG**	• ↑ **QT interval**[18,19] (additive effect) → **monitor ECG** • Inhibition of CYP 2D6 by nilotinib: ↑ trimipramine exposure[9,18,19]
Amitriptyline	• Inhibition of CYP 3A4 and 2D6 by imatinib: ↑ amitriptyline exposure[9,18,19]	• Inhibition of CYP 3A4 by dasatinib: ↑ amitriptyline exposure[9,18,19] • ↑ **QT interval** [18,19](additive effect) → **monitor ECG**	• Inhibition of CYP 3A4 and 2D6 by nilotinib: ↑ amitriptyline exposure[9,18,19] • ↑ **QT interval** [18,19](additive effect) → **monitor ECG**
Phenothiazines			
Levomepromazine	• Inhibition of CYP 2D6 by imatinib: ↑ levomepromazine exposure[9,18,19]	—	• Inhibition of CYP 2D6 by nilotinib: ↑ levomepromazine exposure[9,18,19]
Z-drugs			
Zolpidem	• Inhibition of CYP 3A4 by imatinib: ↑ zolpidem exposure[9,18,19]	• Inhibition of CYP 3A4 by dasatinib: ↑ zolpidem exposure[9,18,19]	• Inhibition of CYP 3A4 by nilotinib: ↑ zolpidem exposure[9,18,19]
Zaleplon	• Inhibition of CYP 3A4 by imatinib: ↑ zaleplon exposure[9,18,19]	• Inhibition of CYP 3A4 by dasatinib: ↑ zaleplon exposure[9,18,19]	• Inhibition of CYP 3A4 by nilotinib: ↑ zaleplon exposure[9,18,19]
Zopiclon	• Inhibition of CYP 3A4 by imatinib: ↑ zopiclon exposure[9,18,19]	• Inhibition of CYP 3A4 by dasatinib: ↑ zopiclon exposure[9,18,19]	• Inhibition of CYP 3A4 by nilotinib: ↑ zopiclon exposure[9,18,19]
Benzodiazepines			
Alprazolam	• Inhibition of CYP 3A4 by imatinib: ↑ alprazolam exposure[9,18,19]	• Inhibition of CYP 3A4 by dasatinib: ↑ alprazolam exposure[9,18,19]	• Inhibition of CYP 3A4 by nilotinib: ↑ alprazolam exposure[9,18,19]
Bromazepam	• Inhibition of CYP 3A4 by imatinib: ↑ bromazepam exposure[9,18,19]	• Inhibition of CYP 3A4 by dasatinib: ↑ bromazepam exposure[9,18,19]	• Inhibition of CYP 3A4 by nilotinib: ↑ bromazepam exposure[9,18,19]
Clonazepam	• Inhibition of CYP 3A4 by imatinib: ↑ clonazepam exposure[9,18,19]	• Inhibition of CYP 3A4 by dasatinib: ↑ clonazepam exposure[9,18,19]	• Inhibition of CYP 3A4 by nilotinib: ↑ clonazepam exposure[9,18,19]
Oxazepam	—	—	—
Lorazepam	—	—	—
Diazepam	• Inhibition of CYP 3A4 by imatinib: ↑ diazepam exposure[9,18,19]	• Inhibition of CYP 3A4 by dasatinib: ↑ diazepam exposure[9,18,19]	• Inhibition of CYP 3A4 by nilotinib: ↑ diazepam exposure[9,18,19]
Midazolam	• Inhibition of CYP 3A4 by imatinib: ↑ midazolam exposure[9,18,19] • Inhibition of Pgp by midazolam: ↑ imatinib exposure[9,18,19] • Inhibition of hOCT1 by midazolam: ↓ imatinib intracellular exposure[9,18,64]	• Inhibition of CYP 3A4 by dasatinib: ↑ midazolam exposure[9,18,19] • Inhibition of Pgp by midazolam: ↑ dasatinib exposure[9,18,19]	• Inhibition of CYP 3A4 by nilotinib: ↑ midazolam exposure[9,18,19]
Barbiturates			
Phenobarbital	• Inhibition of CYP 2C9 and 2C19 by imatinib: ↑ phenobarbital exposure[9,18,19] • **Induction of CYP 3A4 by phenobarbital: ↓ imatinib exposure**[9,18,19]	• **Induction of CYP 3A4 by phenobarbital: ↓ dasatinib exposure**[9,18,19]	• Inhibition of CYP 2C9 by nilotinib: ↑ phenobarbital exposure[9,18,19] • **Induction of CYP 3A4 by phenobarbital: ↓ nilotinib exposure**[9,18,19]
Antipsychotic agents			
Haloperidol	• Inhibition of CYP 3A4 and 2D6 by imatinib: ↑ haloperidol exposure[9,18,19]	• Inhibition of CYP 3A4 by dasatinib: ↑ haloperidol exposure[9,18,19] • ↑ **QT interval**[18,19] (additive effect) → **monitor ECG**	• ↑ **QT interval** [18,19] (additive effect) → **monitor ECG**

Part 8. Nervous system (continued)

	Imatinib	Dasatinib	Nilotinib
Clozapine	• Inhibition of CYP 3A4 and 2D6 by imatinib: ↑ clozapine exposure[9,18,19]	• Inhibition of CYP 3A4 by dasatinib: ↑ clozapine exposure[9,18,19]	• Inhibition of CYP 3A4 and 2D6 by nilotinib: ↑ clozapine exposure[9,18,19]
Olanzapine	—	—	—
Risperidone	• Inhibition of CYP 2D6 by imatinib: ↑ risperidone exposure[9,18,19]	• **↑ QT interval**[18,19] (additive effect) **→ monitor ECG**	• **↑ QT interval**[18,19] (additive effect) **→ monitor ECG**
Antiseizure drugs			
Phenytoin	• **Induction of CYP 3A4 by phenytoin:** **↓ imatinib exposure** [9,18,19]	• **Induction of CYP 3A4 by phenytoin:** **↓ dasatinib exposure** [9,18,19]	• **Induction of CYP 3A4 by phenytoin:** **↓ nilotinib exposure** [9,18,19]
Valproic acid	• Inhibition of CYP 2C9 and 2C19 by imatinib: ↑ valproic acid exposure • Inhibition of CYP 3A4 by valproic acid: ↑ imatinib exposure[9,18,19]	• Inhibition of CYP 3A4 by valproic acid: ↑ dasatinib exposure[9,18,19]	• Inhibition of CYP 2C9 by nilotinib: ↑ valproic acid exposure •Inhibition of CYP 3A4 by valproic acid: ↑ nilotinib exposure[9,18,19]
Carbamazepine	• **Induction of CYP 3A4 and Pgp by carbamazepine:** **↓ imatinib exposure**[9,18,19]	• **Induction of CYP 3A4 and Pgp by carbamazepine:** **↓ dasatinib exposure**[9,18,19]	• **Induction of CYP 3A4 by carbamazepine:** **↓ nilotinib exposure**[9,18,19]
Lamotrigine	—	—	—
Gabapentin	—	—	—
Topiramate	• Induction of CYP 3A4 by topiramate: ↓ imatinib exposure[9,18,19]	• Induction of CYP 3A4 by topiramate: ↓ dasatinib exposure[9,18,19]	• Induction of CYP 3A4 by topiramate: ↓ nilotinib exposure[9,18,19]
Levetiracetam	—	—	—
Antimaniac drug			
Lithium	—	—	—
Aminoketone			
Bupropion	—	—	• **Induction of CYP 2B6 by nilotinib:** **↓ bupropion exposure** **↑ bupropion bioactivation**[9,18,19]
Opioids			
Morphine	—	—	—
Tramadol	• Inhibition of CYP 3A4 and 2D6 by imatinib: ↑ tramadol exposure[9,18,19] ↓ tramadol bioactivation[9,18,19]	• Inhibition of CYP 3A4 by dasatinib: ↑ tramadol exposure[9,18,19]	• Inhibition of CYP 3A4 and 2D6 by nilotinib: ↑ tramadol exposure[9,18,19] ↓ tramadol bioactivation[9,18,19]
Methadone	• Inhibition of CYP 3A4 by imatinib: ↑ methadone exposure[9,18,19] • Inhibition of Pgp by methadone: ↑ imatinib exposure[9,18,19]	• **↑ QT interval**[18,19] (additive effect) **→ monitor ECG** • Inhibition of CYP 3A4 by dasatinib: ↑ methadone exposure[9,18,19] • Inhibition of Pgp by methadone: ↑ dasatinib exposure[9,18,19]	• Inhibition of CYP 3A4 by nilotinib: ↑ methadone exposure[9,18,19] • **Induction of CYP 2B6 by nilotinib:** **↓ methadone exposure**[19] • **↑ QT interval**[18,19] (additive effect) **→ monitor ECG**
Hydromorphone	—	—	—
Oxycodone	• Inhibition of CYP 3A4 and 2D6 by imatinib: ↑ oxycodone exposure ↓ oxycodone bioactivation[9,18,19]	• Inhibition of CYP 3A4 by dasatinib: ↑ oxycodone exposure[9,18,19]	• Inhibition of CYP 3A4 and 2D6 by nilotinib: ↑ oxycodone exposure ↓ oxycodone bioactivation[9,18,19]
Buprenorphine	• Inhibition of CYP 3A4 by imatinib: ↑ buprenorphine exposure[9,18,19]	• Inhibition of CYP 3A4 by dasatinib: ↑ buprenorphine exposure[9,18,19]	• Inhibition of CYP 3A4 by nilotinib: ↑ buprenorphine exposure[9,18,19]
Other			
Acetaminophen	• **Inhibition of O-glucuronidation by imatinib:** **↑ acetaminophen exposure**[9,18,19,50]	—	—
Antimigraine preparations			
Dihydroergotamine	• Inhibition of CYP 3A4 by imatinib: ↑ dihydroergotamine exposure[9,18,19]	• Inhibition of CYP 3A4 by dasatinib: ↑ dihydroergotamine exposure[9,18,19]	• Inhibition of CYP 3A4 by nilotinib: ↑ dihydroergotamine exposure[9,18,19]
Sumatriptan	—	—	—

patients homozygous for the UGT1A1*28 reduced-function variant).[60] The determination of UGT1A1*28 is therefore approved by the Food and Drug Administration as a valid pharmacogenetic test for patients treated by nilotinib.[61] This TKI is ~ 98% bound to albumin and α1-acid glycoprotein.[54]

Nilotinib exposure is expected to increase under CYP3A4 inhibitors. For example, AUC of nilotinib was increased by a 3-fold factor in healthy subjects receiving ketoconazole.[12] Moreover, a study showed that concurrent intake of 240 mL of grapefruit juice increased by 60% nilotinib AUC. Concomitant administration of nilotinib with grapefruit juice is therefore not recommended.[62]

Conversely, concomitant administration of CYP3A4 inducers such as rifampicin leads to a reduction by a 4.8 factor in nilotinib exposure.[12,13,42]

Literature about interactions involving protein binding were lacking for nilotinib.

The same potential clinically significant interactions with imatinib and dasatinib can occur with nilotinib. For example, acenocoumarol and phenprocoumon, substrates of CYP2C9, show increased concentrations, imposing careful monitoring of prothrombin time or international normalized ratio.[9] Moreover, as with dasatinib, nilotinib has been associated with prolongation of the QTc interval, and cases of sudden cardiac death have

Part 9. Respiratory system

	Imatinib	Dasatinib	Nilotinib
H1-antagonists			
Cetirizin	—	—	• Inhibition of Pgp by nilotinib: ↑ cetirizin exposure[9,18,19]
Levocetirizin	—	—	• Inhibition of Pgp by nilotinib: ↑ levocetirizin exposure[9,17,18]
Loratadin	• Inhibition of CYP 3A4 by imatinib: ↑ loratadin exposure[9,18,19]	• Inhibition of CYP 3A4 by dasatinib: ↑ loratadin exposure[9,18,19]	• Inhibition of Pgp by nilotinib: ↑ loratadin exposure[9,18,19]
Fexofenadin	• Inhibition of Pgp by fexofenadin: ↑ imatinib exposure[64] • Inhibition of Pgp by imatinib: ↑ fexofenadin exposure[64]	• Inhibition of Pgp by fexofenadin: ↑ dasatinib exposure[64]	• Inhibition of Pgp by nilotinib: ↑ fexofenadin exposure[64]
Anti-asthma drugs			
Salbutamol	—	—	—
Theophylline	—	—	—

Part 10. Miscellaneous

	Imatinib	Dasatinib	Nilotinib
St John's wort	• **Induction of CYP 3A4 by St John's wort: ↓ imatinib exposure**[43,44]	• **Induction of CYP 3A4 by St John's wort: ↓ dasatinib exposure**[56]	• Induction of CYP 3A4 by St John's wort: ↓ nilotinib exposure[9,18]
Grapefruit	• Inhibition of CYP 3A4 and Pgp by grapefruit: ↑ imatinib exposure [9,18]	• Inhibition of CYP 3A4 and Pgp by grapefruit: ↑ dasatinib exposure [9,18]	• **Inhibition of CYP 3A4 by grapefruit: ↑ nilotinib exposure**[62]
Licorice	• Inhibition of CYP 3A4 by licorice: ↑ imatinib exposure[9,18,89]	• Inhibition of CYP 3A4 by licorice: ↑ dasatinib exposure[9,18,89]	• Inhibition of CYP 3A4 by licorice: ↑ nilotinib exposure[9,18,89]

been reported.[58,59] Accordingly, nilotinib prescribing information includes a black box warning about the risk of QTc prolongation and sudden death and warns that nilotinib should not be used in patients with hypokalemia, hypomagnesemia, or long QT syndrome, either congenital or drug induced.[58,59]

Conclusions

Pharmacokinetics, drug interactions, and safety recommendations are best characterized for imatinib, which was the first TKI on the market. The other TKIs, just recently marketed, have so far only a limited documentation about clinically relevant interactions. Their concentration profile might be affected to a more dramatic degree by interactions than imatinib exposure.

The 3 TKIs reviewed are indeed substrates of several drug transporters and metabolizing enzymes. They are also capable of inhibiting drug transporters and enzymes, making their disposition and metabolism rather complex and difficult to predict.

Most of the available pharmacokinetic information is based on information obtained from in vitro experiments, animal studies, drug–drug interaction studies, and studies in healthy volunteers with a single dose of the aimed TKI. These results must be translated into treatment adjustment recommendations for the clinical oncology practice, where these drugs are administered on a daily basis in patients receiving various co-medications. The actual relevance of predicted drug interactions is thus still uncertain. Most of the interactions outlined in Table 1 (except those in boldface) are theoretical and have not been confirmed in clinical studies; therefore, they should only be considered indicative. Further interaction mechanisms may still be unknown at present.

We advise the reader to regularly monitor for updates about this topic. Therapeutic Drug Monitoring of TKIs[63] should be considered if a drug interaction is suspected, or in case of toxicity, or lack of satisfactory clinical response. Finally, documenting unexpected observations and reporting them to the Pharmacovigilance network is of definite importance.

Authorship

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