Drug Interactions with Tyrosine Kinase Inhibitors

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Dasatinib (Sprycel), erlotinib (Tarceva), gefitinib (Iressa), imatinib (Gleevec), lapatinib (Tykerb), nilotinib (Tasigna), pazopanib (Votrient), sorafenib (Nexavar), and sunitinib (Sutent) are tyrosine kinase inhibitors (TKIs). They are indicated for the treatment of a variety of malignancies, due to their ability to interfere with cell communication and growth.

Each of these agents is metabolized by cytochrome P450 3A4 (CYP3A4) to a significant degree. Some also undergo metabolism via other CYP enzymes, including CYP1A2 (imatinib, erlotinib) and CYP1C19 (imatinib, lapatinib). Most are also substrates for various efflux transporters, including P-glycoprotein and organic cation transporters. This review will focus on interactions that affect TKI metabolism.

> Few data are available detailing the effects of commonly used drugs that modify CYP3A4 activity.

The Effect of Enzyme Inhibitors on TKIs

Whereas strong inhibitors of CYP3A4, such as ketoconazole, affect the clearance of all TKIs, some (eg, dasatinib, lapatinib) are markedly sensitive to the inhibitors, with 3- to 5-fold increases in their mean area under the concentration time curve (AUC). Sorafenib is unique in that it does not appear to be very susceptible to enzyme inhibitors or inducers. This may be due to its partial metabolism by glucuronidation pathways.

Table 1

CYP3A4 Inhibitors	
Amiodarone	Indinavir
Amprenavir	Itraconazole
Aprepitant	Nelfinavir
Atazanavir	Posaconazole
Clarithromycin	Quinupristin-dalfopristin
Conivaptan	Ritonavir
Cyclosporine	Saquinavir
Darunavir	Telithromycin
Delavirdine	Verapamil
Diltiazem	Voriconazole
Erythromycin	

Table 1 lists other known CYP3A4 inhibitors. Although no data exist for TKI interactions with most of these agents, one should assume that the plasma concentration of TKIs will be increased during concurrent administration of these agents.

Patients receiving a TKI should be monitored for increasing side effects (anemia, neutropenia, folliculitis, skin rash, edema, nausea, vomiting, and diarrhea) if an inhibitor of CYP3A4 is coadministered.

The Effect of Enzyme Inducers on TKIs

Rifampin is an inducer of most CYP450 enzymes and has been shown to reduce the AUC of most TKIs. The magnitude of decrease in the TKI plasma concentration is likely to reduce or eliminate its therapeutic effect. Concurrent administration of rifampin would likely require an increase in the dosage of the TKI. Watch for toxicity when rifampin is discontinued in these patients if no concurrent dose reduction is employed.

Table 2

CYP3A4 Inducers	
Bosentan	Phenobarbital
Carbamazepine	Phenytoin
Dexamethasone	Primidone
Efavirenz	Rifabutin
Fosphenytoin	Rifampin
Nafcillin	Rifapentine
Nevirapine	St. John's wort
Oxcarbazepine	

Table 2 lists other known CYP3A4 inducers. Pending data defining the magnitude of these potential precipitant drugs on TKI concentrations, one should assume that they will produce an important reduction in TKI activity.

Despite the obvious sensitivity of the TKIs to inhibitors and inducers of CYP3A4, few data are available detailing the effects of commonly used drugs that modify CYP3A4 activity. It is important that pharmacists inform prescribers of potential TKI interactions with interacting prescription products and counsel patients regarding the possible risks associated with the use of OTC drugs such as St. John's wort. ■

More on the Web

For a list of references and a table on drug interactions with tyrosine kinase inhibitors, go to **www.PharmacyTimes.com/issue/pharmacy/2010/April2010.**

Table

Drugs Reported to Interact with Tyrosine Kinase Inhibitors			
Object Drug	***Inhibitor***	***Inducer***	***Comments***
Dasatinib	Ketoconazole		5-fold ↑ AUC
		Rifampin	>80% ↓ AUC
Erlotinib	Ketoconazole		>85% ↑ AUC
		Rifampin	>80% ↓ AUC
		Smoking	Smokers have 65% lower AUC than nonsmokers
Gefitinib	Itraconazole		60-80% ↑ AUC
		Rifampin	>80% ↓ AUC
Imatinib	Ketoconazole		80% ↑ AUC
		Rifampin	75% ↓ AUC
		St. John's wort	30% ↓ AUC
Lapatinib	Ketoconazole		3.6-fold ↑ AUC
		Carbamazepine	75% ↓ AUC
Nilotinib	Ketoconazole		3-fold ↑ AUC
		Rifampin	80% ↓ AUC
Pazopanib	Ketoconazole		3-fold ↑ AUC of pazopanib eye drops
Sorafenib	Ketoconazole		No change in AUC
		Rifampin	37% ↓ AUC
Sunitinib	Ketoconazole		50% ↓ AUC
		Rifampin	45% ↓ AUC

AUC = area under the concentration time curve.