Enzyme- and Transporter-Mediated Drug Interactions with Small Molecule Tyrosine Kinase Inhibitors

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Received 20 May 2014; revised 11 July 2014; accepted 14 July 2014

Published online in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/jps.24113

ABSTRACT: Among the novel and target-specific classes of anticancer drugs, small molecule tyrosine kinase inhibitors (TKIs) represent an extremely promising and rapidly expanding group. TKIs attack cancer-specific targets and therefore have a favorable safety profile. However, as TKIs are taken orally along with other medications on a daily basis, there is an elevated risk of potentially significant drug–drug interactions. Most TKIs are metabolized primarily through CYP3A4. In addition, many TKIs are also CYP3A4 inhibitors at the same time. In addition to drug metabolizing enzymes (DMEs), another determinant of TKI disposition are drug transporters. There is accumulating evidence showing that the majority of currently marketed TKIs interact with ATP-binding cassette transporters, particularly P-glycoprotein as well as Breast Cancer Resistance Protein and serve as both substrates and inhibitors. Considering the dual roles of TKIs on both DMEs and drug transporters, and the importance of these enzyme and transporters in drug disposition, the potential for enzyme- and transporter-mediated TKI–drug interactions in patients with cancer is an important consideration. This review provides a comprehensive overview of drug interactions with small molecule TKIs mediated by DMEs and drug transporters. The TKI–drug interactions with TKIs being victims and/or perpetrators are summarized. © 2014 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci
Keywords: ADME; clinical pharmacokinetics; drug interactions; membrane transporter; drug metabolizing enzymes; cancer chemotherapy

INTRODUCTION

Patients with cancer, more often than not, are treated with multiple medications. Accordingly, this population is more susceptible to potential drug–drug interactions (DDIs). In addition to primary anticancer agents, complementary alternative therapies and other supportive care drugs are often utilized.[1,2] In addition, it has been reported that around 60% of cancer patients are elderly people (>65 years) and up to 80% of this group have co-morbid conditions, such as cardiovascular disorders, neuropsychiatric disorders, respiratory disorders, digestive disorders, arthritis, and others.[3,4] All of these coexisting diseases require management with corresponding medications, which can subsequently lead to the increased risk of DDIs.[5] Finally, at least one report has suggested that DDIs may be the cause of death in up to 4% of cancer patients.[6]

In addition to the above factors, the increase in the use and availability of oral anticancer agents in the recent years represents an important and new factor that can further increase the potential for DDIs. The landscape of the cancer treatment has changed considerably in the past 15 years and conventional cytotoxic agent is no longer the only cornerstone of cancer chemotherapy.[7–9] With the rapid expansion of knowledge surrounding the molecular mechanisms underpinning cancer pathogenesis, a number of recently approved anticancer drugs have been designed to block the fundamental mutations that cause specific cancers, such as aberrant growth factor receptors, dysregulated intracellular signaling pathways, defective DNA pair, and tumor angiogenesis, and others.[10,11] These molecularly targeted therapies represent an entirely new class of anticancer therapeutic.[8] Unlike conventional chemotherapy that is typically nondiscriminating in damaging both normal and cancerous cells and often produce a variety of potentially severe side effects, these novel targeted anticancer drugs attack cancer-specific targets and therefore have a more favorable safety profile. In contrast to conventional cytotoxic agents that are usually given intravenously on a weekly or even less-frequent basis, molecularly targeted therapy can be taken orally on a daily basis because of their low toxicity profile.[9,12] These orally administered, novel, and targeted anticancer drugs offer greater convenience to patients by avoiding the necessity for invasive intravenous administration and may also be associated with better quality of life. Furthermore, these agents have a much more favorable side effect profile. However, despite these benefits, it is important to keep in mind that these targeted anticancer drugs are taken orally along with other medications on a daily basis and therefore may have higher chance of DDI than those conventional cytotoxic drugs.

Drug–drug interactions are generally viewed as falling into one of three main categories: pharmaceutic, pharmacodynamics (PD), and pharmacokinetic (PK). Pharmaceutic DDIs

Abbreviations used: DDIs, drug–drug interactions; TKIs, tyrosine kinase inhibitors; ABC transporters, ATP-binding cassette transporters; P-gp, P-glycoprotein; BCRP, breast cancer resistance protein; BCR—ABL, breakpoint cluster region—ABL; EGFR, epidermal growth factor receptor; VEGFR, vascular endothelial growth factor receptor; PDGFR, platelet-derived growth factor receptor; HGFR, hepatocyte growth factor receptor; ALK, anaplastic lymphoma kinase; RET, rearranged during transformation; FGFR, fibroblast growth factors receptor; OATP, organic anion-transporting polypeptide; OAT, organic anion transporter.

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Journal of Pharmaceutical Sciences

typically involve issues of incompatibility of medications utilized in parenteral products, such as intravenous fluids, and are generally governed by the physiochemical properties of the involved drugs, nutritional additives, and/or diluents and typically involve such processes as drug complexation or precipitation. PD DDIs are those that alter the pharmacological activity of therapeutic medications, which may result in antagonistic, additive, or even synergistic effects upon one or more interacting drug. PK DDIs may alter one or more of the aspects affecting drug absorption, distribution, metabolism, and excretion (i.e., ADME). These types of DDIs are the primary focus of the present review.

Drug metabolic pathways are generally subdivided into two phases. Phase I (functionalization) reactions result in products containing new or modified functional groups. Oxidative pathways dominate phase I processes. Reductive and hydrolytic pathways are also included in phase I reactions. The majority of marketed medications are metabolized to varying extents by the cytochrome P450 (CYP) mixed-function oxidase system. The CYP enzyme system is a supergene family with more than a dozen prominent enzymes.[13] The primary isoforms of interest in human drug metabolism include CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4.[14] The majority of these enzymes may be induced or inhibited to varying degrees by various coadministered medications, dietary compounds, and environmental factors.

In addition to pharmaceutic, PD, and PK DDIs, drug transporters including uptake and efflux transporters are increasingly appreciated as important determinants in the ultimate disposition and plasma and tissue concentrations of substrate drugs.[15] Drug transporters are localized in organs such as small intestine, liver, and kidney, which are critical for drug absorption and elimination. Moreover, efflux transporters can be found in important blood–tissue barriers such as the blood–brain barrier. As documented with CYP450 enzymes, inhibition or induction of drug transporters can occur as a consequence of coadministration drugs and dietary substances as well as exposure to certain environmental factors. Such interactions can likewise alter the ultimate PK disposition, and in some instances, PD effects of specific substrate drugs.

Among the novel and target-specific classes of anticancer drugs, small molecule tyrosine kinase inhibitors (TKIs) represent an extremely promising and rapidly expanding group.[16] Following the initial approval of imatinib by the United States Food and Drug Administration (US FDA) in 2001, approach 20 TKIs targeting different tyrosine kinases have been approved for clinical use (Fig. 1), and numerous others are in various phases of clinical investigation. Most TKIs have been found to be metabolized primarily through CYP3A4,[17] a major CYP450 enzyme that is highly expressed in both intestine and liver and is known to be responsible for approximately 50% of all marketed drugs that are eliminated via metabolism. Therefore, there is a high potential for interactions between TKIs and other drugs that are coadministered by patients with cancer. For all TKIs that have been approved by the US FDA, the impact of strong CYP3A4 metabolic inhibitors (such as ketoconazole) and/or inducers (such as rifampin) on the disposition of TKIs has been evaluated in human by the respective pharmaceutical company sponsors who developed them. Although numerous TKIs have been reported to be CYP3A4 substrates, many of them, including imatinib, dasatinib, lapatinib, and nilotinib, crizotinib, pazopanib, and regorafenib, are CYP3A4 inhibitors at the same time.[18] For several TKIs that demonstrated CYP3A4 inhibitory effect *in vitro*, their effect on CYP3A4 probe substrates (such as midazolam) have been evaluated as well. Because of the dual roles of TKIs on CYP3A4, when TKIs are coadministered with other drugs, TKIs may not only be the "victims" but also act as "perpetrators" to influence the disposition of coadministered drugs that share this common metabolic pathway. In addition to CYP3A4, other drug metabolizing enzymes (DMEs) that are known to participate in TKI metabolism to varying degrees include CYP2A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, UGT1A1, and UGT1A9.

In addition to DMEs, another determinant of TKI disposition are drug transporters. There is accumulating evidence showing that the majority of currently marketed TKIs are substrates of ATP-binding cassette (ABC) transporters (also known as efflux transporters), particularly P-glycoprotein (P-gp) as well as Breast Cancer Resistance Protein (BCRP).[19,20] It is well known that both P-gp and BCRP are expressed in a number of normal tissues, including intestine and liver, and play key roles in drug absorption, distribution, and elimination.[21] Therefore, there is a high potential for interactions between TKIs and coadministered drugs that have modulatory effects on P-gp and/or BCRP. Interestingly, similar to the interaction of TKIs with CYP3A4, TKIs also have dual roles on efflux transporters—in addition to serving as substrates of P-gp and BCRP, most TKIs are also inhibitors of these two efflux transporters.[19] Considering the dual roles of TKIs on both DME (mainly CYP3A4) and drug transporters (mainly P-gp and BCRP), and the importance of these enzyme and transporters in drug disposition, there is a huge potential for enzyme- and transporter-mediated TKI–drug interactions in patients with cancer.

In the present review, we cover recent findings on enzyme- and transporter-mediated PK interactions between small molecule TKIs and coadministered medications. In addition to CYP3A4, P-gp, and BCRP, TKI–drug interactions mediated by several other DMEs and transporters are also discussed. The TKI–drug interactions with TKIs being victims and/or perpetrators are summarized. Other than DMEs and transporters, the PK interactions that are mediated by other mechanisms are not covered here. In addition, the PD interactions between TKIs and other therapeutic compounds, another type of interaction observed for some TKIs when they are coadministered with conventional cytotoxic agents, are also beyond the scope of this review.

PK SUMMARY OF THE SMALL MOLECULE TKIs

Tyrosine Kinases as Targets for Anticancer Agents

Because of advances in understanding the molecular basis of malignant transformation, current cancer chemotherapy development centers on target-based approaches.[7] Among several targets identified in cancer, tyrosine kinase is the one being exploited the most.[7,8,22] Tyrosine kinases play central roles in diverse biological processes, such as control of cell growth, differentiation, and apoptosis.[22–24] Tyrosine kinases are divided into two main families: proteins that have an extracellular ligand-binding domain (i.e., receptor tyrosine kinases) and proteins that are confined to the cytoplasm or nuclear cellular compartment (i.e., nonreceptor tyrosine kinases). Among the 90 tyrosine kinase genes identified in the human genome to date, 58 encode receptor tyrosine kinases and 32 encode nonreceptor tyrosine