Drug–drug interactions with tyrosine-kinase inhibitors: a clinical perspective

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In the past decade, many tyrosine-kinase inhibitors have been introduced in oncology and haemato-oncology. Because this new class of drugs is extensively used, serious drug–drug interactions are an increasing risk. In this Review, we give a comprehensive overview of known or suspected drug–drug interactions between tyrosine-kinase inhibitors and other drugs. We discuss all haemato-oncological and oncological tyrosine-kinase inhibitors that had been approved by Aug 1, 2013, by the US Food and Drug Administration or the European Medicines Agency. Various clinically relevant drug interactions with tyrosine-kinase inhibitors have been identified. Most interactions concern altered bioavailability due to altered stomach pH, metabolism by cytochrome P450 isoenzymes, and prolongation of the QTc interval. To guarantee the safe use of tyrosine-kinase inhibitors, a drugs review for each patient is needed. This Review provides specific recommendations to guide haemato-oncologists, oncologists, and clinical pharmacists, through the process of managing drug–drug interactions during treatment with tyrosine-kinase inhibitors in daily clinical practice.

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Introduction

To improve effectiveness and reduce adverse events of cancer treatment, specific targets have been identified in oncology in the past decade. One of the most promising groups in targeted therapy are the tyrosine-kinase inhibitors.[1] Tyrosine kinases are key components of signal transduction pathways in the cell that relay information about conditions in the extracellular domain or the cytoplasm to pass on to the nucleus. As a result, tyrosine-kinase inhibitors affect gene transcription and DNA synthesis. Many tumour cells show abnormal activity of specific tyrosine kinases and are therefore an appealing target in oncology.[1]

All tyrosine-kinase inhibitors are given orally, which makes administration flexible and convenient, and improves quality of life. Another advantage of oral administration is that the tyrosine-kinase inhibitors are often taken on a continuous daily basis (compared with intermittent use of most chemotherapy), which usually improves the exposure time of the tumour to the active drug.

Although tyrosine-kinase inhibitors have some advantages compared with traditional chemotherapy, new challenges have arisen in the use of these novel targeted drugs. First, tyrosine-kinase inhibitors have specific toxicity profiles that differ from those of cytotoxic drugs.[2] Toxic effects can be severe (eg, cardiovascular side-effects) and some tyrosine-kinase inhibitors can even cause secondary tumours (eg, vemurafenib). Because the tyrosine-kinase inhibitors are used chronically and are metabolised by cytochrome P450 (CYP) isozymes, patients given these drugs are at substantial risk of having drug–drug interactions. Furthermore, because of the oral administration route of tyrosine-kinase inhibitors, new drug–drug interactions concerning gastrointestinal absorption have become apparent (eg, cotreatment with proton pump and tyrosine-kinase inhibitors).

Drug–drug interactions might be associated with serious or even fatal adverse events, or can lead to reduced therapeutic effects of either drug. Interactions can be classified into those that are pharmacokinetic and those that are pharmacodynamic.[3] Pharmacokinetic interactions arise when absorption, distribution, metabolism, or elimination of the involved drugs are altered, leading to changes in the amount and duration of drug availability at receptor sites. The most common pharmacokinetic drug–drug interactions concern absorption (incomplete drug absorption is a risk of drug interaction) and metabolisation by the cytochrome P450 isozymes. Pharmacodynamic interactions usually refer to an interaction in which active compounds change each other's pharmacological effect. The effect can be synergistic, additive, or antagonistic.

In this Review we give an overview of existing data of known or suspected drug–drug interactions between tyrosine-kinase inhibitors approved by the US Food and Drug Administration or the European Medicines Agency and conventional prescribed drugs, over-the-counter drugs, and herbal medicines. Furthermore, we provide specific recommendations to guide oncologists, haemato-oncologists, and clinical pharmacists through the process of managing drug–drug interactions during treatment with tyrosine-kinase inhibitors in daily clinical practice.

Pharmacokinetic drug interactions: absorption

Gastrointestinal absorption of a drug depends on its inherent characteristics (eg, solubility), but can also be affected by drug–drug interactions. At the absorption level, these interactions mainly take place with tyrosine-kinase inhibitors that have incomplete absorption (eg, bioavailability <50%, first pass effect, or dependence on influx or efflux transporters). Important factors that can affect absorption of tyrosine-kinase inhibitors are a change in stomach pH due to coadministration of an H_2 antagonist, proton-pump inhibitor, or antacid, and the inhibition of P-glycoprotein and intestinal CYP3A4 in enterocytes.

Changes in stomach pH

Besides pH independent, chemical solubility properties, the most important factor that affects solubility and the

resulting exposure to tyrosine-kinase inhibitors is stomach pH.

Because of their weakly basic properties, tyrosine-kinase inhibitors can be present in either the ionised or non-ionised form, depending on the pH in the stomach and the pK_a of the drug (ie, the pH at which the tyrosine-kinase inhibitor reaches equilibrium between the ionised and non-ionised form). Ionised forms normally dissolve more easily than do non-ionised forms. When a tyrosine-kinase inhibitor is coadministered with an acid suppressive drug (eg, a proton-pump inhibitor), the pH in the stomach will increase from 1 to about 4. Subsequently, the equilibrium of ionised or non-ionised drug will shift to the less soluble non-ionised form, and as a result, the bioavailability of the tyrosine-kinase inhibitor will decrease.[4] If the pK_a of a tyrosine-kinase inhibitor (eg, dasatinib) is near the pH range 1–4 the shift towards the non-ionised (less soluble) form, will be greater than that with an inhibitor with a higher pK_a (eg, sunitinib). As such, for tyrosine-kinase inhibitors with a pK_a of less than 4–5, co-administration of acid suppressive drugs (eg, antacids, proton-pump inhibitors, H_2-antagonists) will further reduce solubility and, subsequently, bioavailability and exposure to the tyrosine-kinase inhibitor.

In clinical practice, drug–drug interactions between acid suppressive drugs and tyrosine-kinase inhibitors can be clinically relevant. The oral absorption of crizotinib, dasatinib, erlotinib, gefitinib, lapatinib, and pazopanib is substantially altered by concomitant use of acid suppressive treatment. If possible, the combination of these tyrosine-kinase inhibitors and an H_2-antagonist, proton-pump inhibitor, or antacid should be avoided. Table 1 provides detailed recommendations for the clinical management of these drug–drug interactions.

Inhibition or induction of intestinal enzymes and drug transporters

A tyrosine-kinase inhibitor needs to be transported across the gut wall to reach the portal blood circulation. This transmembrane transport of the drug is a complex multifactorial process mediated by passive diffusion, organic anion and cation transporting peptides, multidrug resistance-associated proteins (eg, ATP-binding cassette [ABC] transporter G2), efflux transporters (eg, P-glycoprotein or multidrug resistance protein 1 [ABCB1]) and intestinal metabolic enzymes (eg, CYP3A4).

After passive diffusion or active transport through the gut lumen (or apical membrane), the tyrosine-kinase inhibitor enters the enterocyte where some tyrosine-kinase inhibitors undergo cytochrome p450 (CYP)-mediated metabolism. Subsequently, the drug or its (active) metabolite will undergo either active countertransport (or efflux) back into the gut lumen, or uptake into the portal vein by passive diffusion, or active transport through the basolateral membrane (figure 1).

P-glycoprotein

The role of P-glycoprotein in the absorption of tyrosine-kinase inhibitors has been widely studied. Some tyrosine-kinase inhibitors (eg, crizotinib) are a substrate for P-glycoprotein, and consequently, inhibition or induction of this efflux transporter by coadministration of another drug might lead to a clinically relevant drug–drug interaction (table 2). Other tyrosine-kinase inhibitors (eg, pazopanib, lapatinib, and gefitinib) directly inhibit the activity of P-glycoprotein and can increase bioavailability of concomitantly used P-glycoprotein substrates. For instance, the area under the curve of digoxin is increased by 80% with P-glycoprotein inhibition by lapatinib.[5,6] Another example is the rise in SN-38 exposure (the active metabolite of irinotecan), which has been attributed to inhibition of P-glycoprotein by lapatinib and gefitinib.[13,14] The increased exposure to paclitaxel (roughly 26%) when used in combination with pazopanib can also be attributed to inhibition of P-glycoprotein by pazopanib.[5,6] Furthermore, the pazopanib area under the curve was increased by 59% with P-glycoprotein-related inhibition of lapatinib. However, at reduced doses of both drugs, no changes were noted in bioavailability.[5,6]

Intestinal CYP3A4

The intestinal metabolic enzyme CYP3A4 exerts its action in close proximity of P-glycoprotein in the enterocytes of the gut lumen (figure 1).[15] Simultaneous use of tyrosine-kinase inhibitors that are substrates for intestinal CYP3A4 together with CYP3A4 inhibitors and inducers can change the exposure and toxicity of tyrosine-kinase inhibitors. An example of a substance that inhibits intestinal CYP3A4 is grapefruit, which increases the area under the curve of sunitinib by 11%, or that of nilotinib by 29%.[16,17] By contrast, grapefruit juice did not seem to affect the area under the curve of imatinib.[18] A possible explanation is that grapefruit juice not only enhances absorption of CYP3A4 substrates at the enterocyte level, but also decreases absorption of organic anion transporting peptides substrates.

Other drug transporters

Besides P-glycoprotein, several tyrosine-kinase inhibitors (eg, imatinib) have been identified as substrates of other drug transporters (eg, organic anion transporting peptides, organic cation transporter, breast cancer resistance protein).[5,6] Some drugs might inhibit organic anion transporting peptides (eg, ciclosporin) or breast cancer resistance protein (eg, lapatinib), but involvement of other mechanisms, such as CYP3A4, cannot be ruled out in these drug–drug interactions.[19] Evidence for drug–drug interactions with tyrosine-kinase inhibitors through inhibition or induction of transporters is not yet available.

Other factors affecting absorption of tyrosine-kinase inhibitors

Another factor that might affect absorption of tyrosine-kinase inhibitors is the formation of an insoluble complex.