Bioavailability of Tyrosine Kinase Inhibitors: An Added Component of Assessment

Kristine Deano Abueg, RN, MSN, OCN®, CBCN®

The growing prominence of tyrosine kinase inhibitors (TKIs) as treatment for malignancies prompts oncology nurses to expand the scope of their patient assessment. Because TKIs as oral agents have a different bioavailability than parenteral agents, factors that alter drug absorption and metabolism can have a measurable effect on the amount of active, available drug when TKIs are prescribed. In relation to TKIs as cancer therapies and intended dosing, this article reviews three drug absorption and metabolism factors: changes in stomach pH, as well as P-glycoprotein and cytochrome P450 interactions.

Factors Affecting Tyrosine Kinase Drug Delivery

The bioavailability of TKIs as oral agents differs from their bioavailability as parenteral agents. Bioavailability is defined as the “rate and extent to which the active ingredient . . . is absorbed from a drug product and becomes available at the site of action” (U.S. Department of Health and Human Services, U.S. Food and Drug Administration [FDA], & Center for Drug Evaluation and Research, 2013, p. 3). More simply, bioavailability is the proportion of administered drug that becomes active.

Parenteral administration is associated with a high rate of bioavailability because IV administration allows for the immediate entry of the administered drug into systemic circulation. In addition, parenteral administration generally is associated with consistent pharmacokinetics and absorption. Oral medications, however, must be absorbed across the gastrointestinal mucosa and processed by gastric and intestinal enzymes, then metabolized in the liver. Along this path, oral medications are transformed from insoluble forms to more absorbable, soluble forms (Polovich, Olsen, & LeFebvre, 2014). Factors that alter drug absorption and metabolism can have a measurable effect on the amount of active, available drug. Three specific altering factors are changes in stomach pH, as well as P-glycoprotein (P-gp) and cytochrome P450 (CYP) interactions.

Changes in Stomach pH

Stomach acidity, measured in pH, has a direct impact on the bioavailability of orally administered agents such as TKIs. Oral medications are formulated to dissolve into soluble, ionized forms at specific pH levels inherent in the human body. Concomitant use of acid-suppressing agents (e.g., proton pump inhibitors [PPIs], H₂ antagonists, antacids) will shift the stomach environment to a higher pH, making it less acidic and, therefore, affecting the chemical availability. For example, erlotinib becomes more soluble in a mildly acidic environment (pH 5.42) (Genentech, 2013). As a PPI, omeprazole will reduce the acidity of the gastric environment and alter the solubility of erlotinib, effectively reducing its chemical availability. The concomitant use of PPIs, such as 40 mg of omeprazole once daily, will decrease the maximum concentration of erlotinib to 61%, which is a dose reduction of 39% (van Leeuwen, van Gelder, Mathijssen, & Jansman, 2014).

Because the concomitant use of acid-reducing agents can adversely affect the accuracy of target dosing of TKIs, patient assessment in oncology nursing has focused on side effects associated with traditional cytotoxic chemotherapeutic agents, including myelosuppression (e.g., neutropenia, thrombocytopenia, anemia), gastrointestinal toxicity (e.g., nausea, vomiting, diarrhea, gastritis), cutaneous toxicity, and constitutional symptoms (e.g., fatigue, pain, malaise). In addition, the assessment for a few drug-specific toxicities has included taxane-induced neuropathy or cisplatin-associated hearing loss.

The growing prominence of tyrosine kinase inhibitors (TKIs) in the oncology pharmaceutical arsenal has triggered a shift in what is considered to be a standard assessment. Targeted therapies have expanded the spectrum of side effects in scope and diversity. Therefore, with targeted therapies, the assessment template includes a wider range of considerations when monitoring and educating patients.
TABLE 1. Examples of Interactions Between Selected TKIs and Acid-Suppressing Agents

<table>
<thead>
<tr>
<th>TKI</th>
<th>Acid-Suppressing Agent</th>
<th>Effective Action of Concentration of TKI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erlotinib</td>
<td>PPI: omeprazole 40 mg daily</td>
<td>Decrease by 61%</td>
</tr>
<tr>
<td></td>
<td>H2 antagonist: ranitidine 150 mg twice daily</td>
<td>Decrease by 17%</td>
</tr>
<tr>
<td>Imatinib</td>
<td>PPI: omeprazole 40 mg daily</td>
<td>No significant effect</td>
</tr>
<tr>
<td></td>
<td>Antacid: aluminum hydroxide, magnesium hydroxide, and simethicone 15 minutes before imatinib</td>
<td>No significant effect</td>
</tr>
<tr>
<td>Nilotinib</td>
<td>PPI: omeprazole 40 mg daily</td>
<td>Decrease by 27%</td>
</tr>
<tr>
<td></td>
<td>H2 antagonist: famotidine (oral) 20 mg twice daily</td>
<td>No significant effect</td>
</tr>
</tbody>
</table>

PPI—proton pump inhibitor; TKI—tyrosine kinase inhibitor
Note. Based on information from U.S. Food and Drug Administration, 2011; van Leeuwen et al., 2014.

P-Glycoprotein Drug Interactions

P-gp is located on the cell membrane of various tissues, including the intestines and liver. As an efflux transporter, P-gp is one of the enzymes responsible for clearing drugs and toxins from cells. The role of P-gp in normal tissue is likely to protect susceptible organs from toxic compounds by limiting their aggregation in the cell. However, P-gp can also efficiently clear aggregated anticancer agents out of the target cell. In vivo studies have reported an overexpression of P-gp, which suggests that cancer cells have an efficient mechanism to clear antineoplastic drugs from themselves (Lin & Yamazaki, 2003).

Many oral agents are known substrates of P-gp and, therefore, are affected by alterations to the function of P-gp. Impeding the ability of P-gp to effectively clear drugs or toxins will result in intracellular accumulation. Conversely, acceleration of the P-gp enzyme will deplete intracellular drug concentration. Providers should be aware of the potential interaction between P-gp inhibitors and substrates.

Atorvastatin is a known inhibitor of P-gp, whereas erlotinib is a known substrate. Atorvastatin will interact with P-gp, slowing the efflux activity of P-gp and causing an accumulation of concomitant erlotinib within the cell. This will likely result in a dosing greater than the target dosing (FDA, 2011). Figure 1 lists examples of P-gp substrates and inhibitors.

Cytochrome P450 Interactions

CYP is a large family of enzymes that is responsible for the metabolism of many drugs. Although this family encompasses more than 50 subtypes, most drug metabolism can be attributed to only six members: CYP1A, CYP2C9, CYP3A5, CYP2C19, and, particularly, CYP3A4 and CYP2D6.

Located primarily in the liver, these enzymes process active drugs into excretable forms (Lynch & Price, 2007). Most drugs are metabolized by a specific CYP enzyme; for example, sunitinib and erlotinib are metabolized by CYP3A4, whereas tamoxifen is metabolized by CYP2D6 (Goetz et al., 2007).

Genetic and environmental factors can affect enzyme activity. Naturally occurring mutations in the gene sequence’s encoding for the CYP enzyme result in a wide variety of effects, from ultrarapid metabolism to the absence of metabolism. For example, mutations in CYP2D6 result in poor metabolism of tamoxifen (Goetz et al., 2007). Environmental factors, such as food and concomitant medications, similarly can affect CYP enzyme activity. Substances that slow the enzyme are called inhibitors, and substances that speed up the enzymes are termed inducers (FDA, 2011). Grapefruit juice is a well-publicized inhibitor of the CYP enzyme CYP3A4, slowing the speed at which it breaks down and processes drugs (Kane & Lipsky, 2000). CYP3A4 is responsible for the metabolism and clearance of sunitinib. The concomitant presence of grapefruit juice (the inhibitor) slows the metabolic activity of CYP3A4, resulting in a backup of the active drug and an increase in sunitinib plasma concentrations (Pfizer, Inc., 2014). Grapefruit juice is considered to be a moderate inhibitor, whereas other medications may have a more pronounced effect. The package insert for sunitinib recommends dose reduction when the drug is coadministered with strong CYP3A4 inhibitors (Pfizer, Inc., 2014).

St. John’s wort, a medicinal herb, is a known inducer of CYP3A4. Concurrent use of St. John’s wort with sunitinib decreases plasma concentrations, resulting in unintended underdosing. The package insert for sunitinib suggests that St. John’s wort may unpredictably decrease sunitinib plasma concentrations. Therefore, patients receiving sunitinib should avoid taking St. John’s wort concomitantly. The insert further recommends that a dose increase for sunitinib should be considered when the drug is...
Medications commonly used in the treatment of cancer pain also frequently involve CYP enzyme metabolism. Opioids, including morphine, hydromorphone, and oxymorphone, are least affected by CYP. However, tramadol relies extensively on two members of the CYP superfamily: CYP3A4 and CYP2D6.

A full discussion of drug-drug interactions specific to analgesics and anticancer therapies is beyond the scope of this article. Nurses are strongly encouraged to work closely with their interdisciplinary teams, including pharmacists and physicians, to ensure optimal pain management in the setting of anticancer drug-drug interactions (Sasu-Tenkoramaa & Fudin, 2013).

The speed of the CYP enzymes affects the processing of drugs in the body. If the CYP enzyme is inhibited, the process is slowed. Conversely, CYP enzyme inducers accelerate induced drug metabolism. Any alteration in drug processing can result in unintended dose modifications. These alterations can lead to toxicity, underdosing, or overdosing, resulting in poor outcomes (FDA, 2010).

**Conclusion**

With the increasing use of TKIs as treatment for malignancies, nurses must broaden the scope of patient assessment. TKIs, used as oral agents, have a markedly different bioavailability than parenteral agents, and factors that alter drug absorption and metabolism can have a significant effect on the amount of active, available treatment. In particular, changes in stomach pH, along with P-gp and CYP interactions, can affect TKI dosing and side-effect management, as well as the overall effectiveness of TKIs as cancer treatments.

**References**


