

ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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Importance of Food Effects for Oral Oncology Drugs



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H&O What factors must be considered when prescribing oral oncology drugs that are not applicable to parenteral administration?

MR Given the multiple steps required to get active drugs from “bottle to blood,” oncologists need to be concerned with adherence, food-drug interactions, and drug-drug interactions. Adherence requires the patient to fill the prescription and then to take the proper dose at the proper time and in the proper context (eg, fasting or with food). Many foods can interact with oral drugs. Some labels require specific meals (eg, not low-fat); in addition, grapefruit juice and cruciferous vegetables are well-established modulators of drug metabolism. Drug-drug interactions are very common, particularly in cancer patients who are taking antidepressants, antibiotics, or antiulcer medications.

Furthermore, the equivalent oral dose of a drug is often significantly less than the parenteral dose, due to first-pass metabolism. This may include metabolism in the intestinal wall and liver, which can be modulated by both foods and other drugs, especially many of the alternative medicines commonly utilized by cancer patients.

H&O What are some of the labeling differences between oral oncology drugs versus non-oncology drugs? What are possible explanations for these differences?

MR Historically, oral drugs have been labeled in a way to maximize bioavailability—the percentage of drug that is in the systemic circulation relative to the same dose administered intravenously. Given that food can be a major determinant of bioavailability, non-oncology drugs whose bioavailability

is improved with food are labeled to be taken with food. However, oncology drugs have generally been labeled with the instruction to take while fasting, even if food markedly increases bioavailability. It is unclear whether this directive is originating in the industry or as a result of regulatory pressures that are being applied to the industry. For example, some US Food and Drug Administration (FDA) officials have published their opinion that cancer patients may have difficulty taking medications with food on a consistent basis.

H&O What are some oral oncology drugs with bioavailability affected by food intake?

MR In recent years, 5 drugs have been approved that are labeled to be taken while fasting, whose bioavailability is increased by food. These drugs are erlotinib (Tarceva, Genentech), lapatinib (Tykerb, GlaxoSmithKline), nilotinib (Tasigna, Novartis), pazopanib (Votrient, GlaxoSmithKline), and abiraterone (Zytiga, Janssen Biotech). The largest food effect is observed with abiraterone, which increases bioavailability up to 10-fold. Patients taking these medications are at risk of effective overdosage if they inadvertently take their medication with food, or eat within a relatively short period after taking the dose. Thus, food intake would expose patients to significant toxicities, including the risk of sudden death observed with nilotinib.

H&O What is the Risk Evaluation & Mitigation Strategy (REMS), and how is it helping to improve the current issues concerning food effects?

MR The Food and Drug Administration Amendments Act of 2007 (FDAAA) gave the FDA new authority

for the regulation of drugs following approval. Prior to the FDAAA, if the FDA had safety concerns, its only unilateral option was to withdraw the drug. However, it can now require a manufacturer to develop a REMS in order to mitigate such concerns. This authority was utilized by the FDA for nilotinib. Like some other drugs, nilotinib can cause QTc prolongation, which is an electrocardiogram (ECG) abnormality that can be associated with sudden death. In order to minimize the risk of QTc prolongation and to monitor for it, the FDA required the creation of a REMS by the manufacturer of nilotinib to make patients and physicians aware of this risk. The goals of the nilotinib REMS are to:

- Minimize the occurrence of QTc prolongation and its potential adverse consequences
- Reduce medication errors involving drug-food interactions and incorrect dosing intervals
- Minimize potential drug-drug interactions
- Inform healthcare providers and patients about the serious risks associated with nilotinib treatment, including QTc prolongation

However, similar REMSs have not been instituted for the other anticancer agents with clinically significant food effects.

H&O Can you discuss the ongoing food effect study of abiraterone in patients with castration-resistant prostate cancer?

MR The University of Chicago is conducting a randomized phase II trial of standard-dose abiraterone (1,000 mg, as labeled) in fasting patients versus low-dose abiraterone (250 mg) administered with food. The study is being led by Dr. Russell Szmulewitz, and is designed to obtain evidence in support of the hypothesis that low-dose abiraterone with food is noninferior to the labeled dose. If this phase II trial meets its goals, it is likely that this hypothesis would be tested further in a full phase III noninferiority study. A lower dose administered with food may also reduce the gastrointestinal toxicity of this agent, resulting in an improve-

ment in the therapeutic index, as well as decrease costs (by approximately \$3,750 per patient every month). Furthermore, successful off-label development of low-dose abiraterone could potentially moderate the pricing of other drugs for this same indication.

H&O What is the biggest remaining challenge in this field?

MR The biggest challenge is obtaining funding for phase IV studies that have the potential for identifying safer and more cost-effective uses of expensive drugs. Historically, such studies have not been of interest to the National Cancer Institute (NCI), and they would not be expected to receive funding from the pharmaceutical industry. Thus, creative funding solutions will be required in order to efficiently conduct such studies, which have the potential to greatly improve the cost-effectiveness of modern anticancer therapy.

Suggested Readings

- ClinicalTrials.gov. A Randomized Phase II Study Evaluating the Food Effect on the Pharmacokinetics and Pharmacodynamics of Abiraterone Acetate in Men With Castrate Resistant Prostate Cancer. <http://clinicaltrials.gov/ct2/show/NCT01543776>. Identifier: NCT01543776.
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