

ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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Food Effects on Oral Agents

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H&O How is research into food effects on oral agents conducted?

LL In cancer, the most reasonable and scientifically rigorous paradigm for conducting research into food effects on oral agents is to use a group of patients with advanced disease and very simplistically administer a standardized oral dose of the drug on one occasion when they are fasting and on another when they have ingested a standardized meal. The drug is taken following the meal in a standardized time-frame. On each of those occasions, having given the medication, the researchers follow the blood concentrations of the drug over a period of approximately 24 hours, usually at several timepoints rapidly after the drug is given and then at longer intervals. The researchers thus generate two exposure curves of plasma concentration versus time. If the patient was similar on those two days with regard to his or her condition, the major difference was the meal eaten with one dose and no meal eaten with another dose. The researcher is enabled to assess the effect of food on the amount of drug that enters the bloodstream.

H&O How did the research on food effects on lapatinib fit into this paradigm?

LL Our phase I study of food effects on lapatinib (Tykerb, GlaxoSmithKline) complicated the paradigm slightly by including two different meals plus a fasting state. We used standardized low- and high-fat meals, and to make the study as rigorous as possible, the same administration process was used on each occasion, with the exception of the different meals. Patients were randomized to three arms in order to vary what accompanied the first dose. Some patients fasted first, then received the low-fat meal, followed by the high-fat meal; others received the low-fat meal first, followed by fasting, followed by the high-fat

meal; and others still received the high-fat meal first, followed by the low-fat meal, followed by fasting. This randomization schedule was intended to minimize any carry-over effects that might occur.

The major objective of the study was to define the effect of food, either a low- or a high-fat meal, on the amount of lapatinib entering the bloodstream. Lapatinib was given to a group of oncology patients who were monitored clinically and who had blood tests to ensure eligibility. During the study, lapatinib concentrations in the blood were measured.

The primary findings of the research were interesting and surprisingly significant. The major effect was that the ingestion of lapatinib with either a high- or low-fat meal produced a significant change in the amount of drug entering the blood. With a low-fat meal, there was an increase of approximately 167%, and with the high-fat meal, the increase was 325%. The amount of drug entering the systemic blood and therefore available to go to the tumor was clearly much different both between the meals and in comparison to the fasting state. The magnitude of the change was surprising to the researchers. It is known that there are some drugs that become a little more bioavailable with food, but not to this degree. Additionally, some drugs can enter the bloodstream in reduced amounts when taken with food, eg, the drug currently approved for use with lapatinib, capecitabine. The currently available data suggest that less capecitabine enters the bloodstream when it is taken with food. This reduction in bioavailability complicates the possibility of studying lapatinib with food and capecitabine without food because they are normally taken together. In our study, patients received lapatinib alone at a single 1,500-mg dose on each occasion. Further research should administer lapatinib on a number of occasions over the course of a week with a regular meal.

H&O What was the rationale to study the effects of food on lapatinib?

LL There were several aspects to the rationale for studying the effects of food on lapatinib. First, preliminary data suggested that there may be a significant effect of food on the pharmacokinetics of this drug, an effect needing to be quantified. Second, lapatinib has been administered without food in virtually all the studies done in breast cancer

in which lapatinib has been combined with capecitabine and shown to be associated with a benefit in comparison to capecitabine alone. Therefore, it was important to define the effect of food, because if it caused major changes in pharmacokinetics, as we discovered, it is necessary to give the patient correct instructions on how to take the drug. We felt it was necessary to look closely at food effects from a practical point of view for the patient receiving the drug, who is at risk of receiving a much higher equivalent dose if she takes the drug with food, potentially leading to more toxicity. Lapatinib's labeling as approved by the US Food and Drug Administration (FDA) indicates that the drug should not be taken within 1 hour of eating. Further studies in this setting will be necessary to see whether the effects of food pertain to different doses of lapatinib before considering the possibility of modifying the current FDA prescribing guidelines.

H&O What is the mechanism of food effects on lapatinib?

LL The mechanism of food effects on lapatinib is unknown thus far, and no single mechanism can be defined as causing the effects of food on bioavailability of lapatinib. The typical mechanisms of food effects are thought to be an increase in blood flow following eating, a change in gastric motility, a change in the gastric milieu, greater solubility of drugs in fat present in food in the gastrointestinal system, and the release of biosecretions that can change drug solubility. Important to consider are the food itself and its composition (ie, fats, carbohydrates, etc.), and the changes that occur in a human after ingestion of food. I speculate the mechanism is likely to be a combination of these simultaneous effects. Based on our data, we cannot tease out one single mechanism. But we are alert to the fact that something significant is happening, and studies in the future may define the exact mechanism.

H&O Are other oral agents good candidates for research on food effects?

LL Yes. There are a number of researchers exploring food and/or dietary effects on drug absorption/bioavailability. We know, for example, that grapefruit juice in particular has the capacity to considerably increase the amount of drug absorbed. Grapefruit juice contains a component that affects CYP3A, both inhibiting the enzyme and possibly downregulating it. The amount of CYP3A in the intestine is reduced, which means that the drug does not break down as much and more passes the liver and enters systemic circulation. The area under the plasma concentration time curve is increased and the systemic exposure is increased. Researchers have been searching for a mechanism by which this effect can be utilized, to use lower doses of drugs where this is a clearcut effect. One avenue

of research is the use of grapefruit juice, for example, to increase absorption and reduce the dose given of very expensive drugs, such as those used in organ-transplant immunosuppression (eg, cyclosporin, tacrolimus, sirolimus). Research in this setting is ongoing, and a multitude of drugs could be affected in this way. In fact, lapatinib is also a CYP3A substrate, and thus the interaction of lapatinib and grapefruit juice could be studied. However, in our study, because of our knowledge of this interaction, we carefully avoided the use of grapefruit juice on the days the patients were being assessed.

H&O Could you discuss potential further studies to define the mechanism of food effects?

LL Further studies into the mechanism of food effects would have a similar design to what I described. However, we need to look at the different components of the food, which may be difficult. One method would be to give the food with certain inhibitors of gastric acid production or with agents that would enhance or reduce biosecretions. To tease out the mechanism would require a complicated series of studies rather than a single study. The easiest single study to perform would probably entail comparing dosing while fasting versus dosing accompanied by grapefruit juice.

H&O What is your view of the recently published commentary "The Value Meal: How to Save \$1,700 Per Month or More on Lapatinib"?

LL Drs. Mark Ratain and Ezra Cohen give accurate information in their commentary, published online by the *Journal of Clinical Oncology*. They argue that it may be possible to decrease the dose, and hence cost, of oral anticancer agents if they are administered with food, increasing their bioavailability. The authors note that they are extrapolating to the possibility of using food to reduce the amount of drug needed. To achieve that reduction, however, there must be further studies before we can change the recommendation on dosing. It is necessary to show that the food effect is consistent and occurs chronically, which means that patients must control what they eat when they take the drug. Also, it will have to be shown that the food effect is of a similar magnitude at lower doses. It may be premature to advocate the position of Drs. Ratain and Cohen in clinical practice without further research, as they recognize.

Suggested Readings

Reddy N, Cohen R, Whitehead B, et al. A phase I, open-label, three period, randomized crossover study to evaluate the effect of food on the pharmacokinetics of lapatinib in cancer patients. *Clin Pharmacol Ther*. 2007;81:S16-S17.

Ratain MJ, Cohen EE. The value meal: how to save \$1,700 per month or more on lapatinib. *J Clin Oncol*. 2007 Jul 16; [Epub ahead of print].