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Avoiding Lapatinib Interactions

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Lapatinib (Tykerb) is a tyrosine kinase inhibitor used in combination with capecitabine in the treatment of HER2-positive advanced breast cancer. Lapatinib has many properties that predispose it to pharmacokinetic drug interactions. A recent article also provided clinical and in vitro evidence suggesting that dexamethasone increases the risk of lapatinib hepatotoxicity.[1]

Interactive Properties

Certain characteristics of lapatinib predispose it to interactions with other drugs. Lapatinib, like other tyrosine kinase inhibitors, is metabolized by cytochrome P450 (CYP) 3A4, and thus is susceptible to interactions with CYP3A4 inhibitors and inducers (as discussed in our April 2010 column).

Lapatinib is also a modest inhibitor of CYP3A4, and probably CYP2C8, although the clinical significance of these effects requires further study. Lapatinib is also both a substrate and an inhibitor of P-glycoprotein, and these properties may result in clinically important drug interactions. Finally, lapatinib has been reported to prolong the QT interval.

CYP3A4 Inducers

Because lapatinib is metabolized primarily by CYP3A4, and dexamethasone is a known CYP3A4 inducer, one would expect that dexamethasone would reduce lapatinib plasma concentrations. Another enzyme inducer, carbamazepine, has been shown to substantially reduce lapatinib concentrations.[2]

But a more sinister possibility has been raised by a study of the effect of dexamethasone on lapatinib hepatotoxicity.[1] In a nested case control study of 120 breast cancer patients taking lapatinib, the risk of hepatotoxicity was almost 5 times higher in those who received dexamethasone concurrently compared with those who did not. It was proposed that lapatinib is converted to a hepatotoxic metabolite by CYP3A4, and dexamethasone enhanced this process.

If this preliminary finding is confirmed, it will be an important clinical concern, because dexamethasone is often the corticosteroid of choice in breast cancer patients with brain metastases. It would also raise the question of whether lapatinib hepatotoxicity could be increased by other enzyme inducers such as carbamazepine (Tegretol), efavirenz (Sustiva), nafcillin (Unipen), nevirapine (Virammune), oxcarbazepine (Trileptal), phenobarbital, phenytoin (Dilantin), primidone (Mysoline), rifabutin (Mycobutin), rifampin (Rifadin), rifapentine (Priftin), and St. John's wort. Stay tuned.

CYP3A4 Inhibitors

Ketoconazole has been shown to increase lapatinib area under the concentration-time curve (AUC) by 3.6-fold, and one would expect that other CYP3A4 inhibitors would also increase lapatinib concentrations. The product information recommends lapatinib dosage reductions if "strong" CYP3A4 inhibitors (eg, ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole) are given concurrently.

Nonetheless, caution is also indicated with "moderate" CYP3A4 inhibitors, including diltiazem, erythromycin, and verapamil, because—due to the high variability of such interactions—a particular patient given a "moderate" inhibitor may develop a large effect on lapatinib.

P-glycoprotein Substrates and Inhibitors

Lapatinib appears to inhibit P-glycoprotein enough to cause clinically important drug interactions. The manufacturer reports an almost 3-fold increase in digoxin AUC due to lapatinib, so one would expect lapatinib to interact with other drugs (eg, colchicine) that are P-glycoprotein substrates. Because lapatinib is also a P-glycoprotein *substrate*, one would expect higher lapatinib concentrations if it is combined with drugs that inhibit P-glycoprotein, but more data are needed on this point.

QT Prolongation

The manufacturer reports dose-dependent prolongation of the QT interval in an uncontrolled, open-label study of 81 advanced cancer patients. The clinical significance of this effect is not clear, but it would be worth monitoring the electrocardiography of patients with other risk factors for QT prolongation, including taking certain other drugs.

Summary

To avoid interactions with lapatinib, it is important to remember that it has the potential for numerous drug interactions with: 1) drugs that are CYP3A4 inhibitors, inducers, or substrates, 2) drugs that are P-glycoprotein inhibitors, inducers, or substrates, 3) possibly drugs that are CYP2C8 substrates, and 4) possibly drugs that prolong the QT interval.

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