Tamoxifen
New Developments

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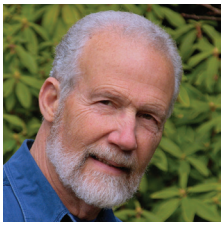
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THE DEBATE ABOUT THE EXTENT TO WHICH CYP2D6 ACTIVITY affects tamoxifen efficacy in patients with breast cancer continues, but the plot has thickened considerably since we last discussed this issue in March 2009. Since then, research papers have continued to appear on both sides of the issue, some suggesting that reduced CYP2D6 activity due to genetics or CYP2D6-inhibiting drugs reduces tamoxifen efficacy, leading to earlier breast cancer relapse and reduced survival, and others failing to find any effect. We also have more evidence that drug interactions involving other tamoxifen metabolic pathways and adenosine triphosphate–binding cassette transporters may also affect tamoxifen efficacy.

CYP2D6 INHIBITORS

CYP2D6 is the most important enzyme in the metabolism of tamoxifen to its primary active metabolite, endoxifen, so it is biologically plausible that the concurrent use of moderate to strong CYP2D6 inhibitors with tamoxifen would inhibit its anticancer effects. Two epidemiological studies published in the past year failed to find any effect of CYP2D6 inhibitors on tamoxifen efficacy,[1,2] but, for the following reasons, it seems unwise to use these results to conclude that we can ignore CYP2D6 inhibitors in patients receiving tamoxifen:

- Other epidemiological studies did in fact find reduced tamoxifen efficacy with CYP2D6 inhibitors,[3-5] so we have evidence on both sides.
- The negative studies had 1 or more significant limitations, such as a short follow-up, using total mortality instead of cancer mortality, and inadequate adjustment for other CYP2D6 inhibitors.
- Epidemiological studies of tamoxifen efficacy are difficult to conduct because of the long period of follow-up required, the many other causes of the outcome (treatment failure), complex CYP2D6 polymorphisms, multiple metabolic pathways for tamoxifen, inability to assess nonadherence, pre- versus postmenopausal patients, lack of tamoxifen dose information, and lack of information on concurrent OTC or herbal medications.[6]

OTHER ENZYMES AND TRANSPORTERS

There is growing evidence that tamoxifen and endoxifen are substrates of P-glycoprotein,[7] which might reduce tamoxifen bioavailability and increase endoxifen efflux from cancer cells. Theoretically, patients with higher P-glycoprotein activity due to genetics or drug therapy would have impaired tamoxifen efficacy. In 1 study, the median time to develop recurrence and metastasis was just 12 months in breast cancer patients with decreased CYP2D6 activity and high P-glycoprotein activity, compared with 48 months in patients with either decreased CYP2D6 or high P-glycoprotein activity alone.[8] So it may be that decreased CYP2D6 activity and increased P-glycoprotein activity can work in concert to impair tamoxifen efficacy.

Enzyme inducers may also be a problem in patients on tamoxifen. In a prospective study, breast cancer patients on tamoxifen were given rifampin 600 mg per day for 15 days.[9] Endoxifen area under the concentration time curve decreased by about 70% after rifampin, leading the researchers to stop the study prematurely to avoid patient harm. The mechanisms for the large reductions in endoxifen concentrations following rifampin are not known and may involve more than 1 pathway. Rifampin is known to induce CYP3A4, CYP2C9, CYP2C19, glucuronidation, and P-glycoprotein, all of which are known to be involved in the disposition of tamoxifen or its metabolites.[10] Until data are available, assume that other enzyme inducers can also reduce endoxifen concentrations.

ENDNOTE

There is too much information suggesting that drug interactions can reduce tamoxifen efficacy. If we assume the interactions are important when they are not, we have taken only a little extra time to avoid certain concurrent medications. Howevere, if we assume there is no interaction when there is, women with breast cancer will have an increased risk of cancer recurrence and death. Therefore, the following recommendations for patients on tamoxifen are prudent:

- Avoid concurrent use of moderate to strong CYP2D6 inhibitors (ONLINE TABLE 1).
- Avoid enzyme inducers (ONLINE TABLE 2).
- Counsel patients on tamoxifen to avoid OTC or herbal drugs that may inhibit CYP2D6 (goldenseal) or induce enzymes (St John's wort). ◆

FOR REFERENCES, GO TO PHARMACYTIMES.COM/LINK/144.