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Drug Interactions and Pharmacogenomics in the Treatment for Breast Cancer and Depression

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Mrs. B is a 45 year old premenopausal female who was diagnosed with major depressive disorder 10 years ago and then successfully treated for 12 months with fluoxetine 20 mg daily without significant side effects from therapy. She remained free of depressive symptoms for the next 8-9 years. One year ago, she was diagnosed with estrogen receptor (ER) positive invasive breast cancer and underwent treatment with surgery, followed by chemotherapy, and then radiation therapy. Mrs. B. has been treated with the selective estrogen receptor modulator (SERM) tamoxifen for the past 6 months to reduce her likelihood of breast cancer recurrence. She has tolerated tamoxifen relatively well, except for moderately bothersome hot flashes for which she has received no pharmacologic therapy. Recently, however, she developed recurrent depressive symptoms and sought treatment from her psychiatrist. What pharmacologic agents are effective against both depression and hot flashes in women with breast cancer? Would any of these agents compromise the efficacy of tamoxifen or increase its toxicity through a drug-drug interaction?

Depression in breast cancer

Many women experience distress following the diagnosis of breast cancer, but a subset experience clinically significant depression (1). The estimated point prevalence of major depressive disorder in all women ranges from 3.5 to 7% (2). In comparison, the rate of depression in women with breast cancer is estimated to be 10-25%, depending on the method of assessment (3). Rates appear higher in the first year following diagnosis, especially in younger women and those treated with chemotherapy (3). Studies evaluating the association between depression and tamoxifen have yielded mixed results. In some trials, a subset of patients have discontinued tamoxifen therapy because of depressive symptoms, whereas other studies, conducted primarily in the breast cancer prevention setting, have not demonstrated an

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increased risk of depression during treatment with tamoxifen (4,5). Therefore, it appears that depression is more common in breast cancer patients, especially in the first year following diagnosis, and that systemic therapies likely influence the development of symptoms.

Endocrine therapy for breast cancer

Approximately 180,000 women are diagnosed with invasive breast cancer in the United States each year (6). The majority of these patients will have tumors that express ER and/or progesterone receptor (PR) on the cell surfaces. Women with hormone receptor-positive tumors obtain substantial benefit from treatment with tamoxifen or agents that decrease circulating levels of estrogen, such as aromatase inhibitors (7). At present, the standard of care for treatment of premenopausal women with ER-positive invasive breast cancer is tamoxifen, whereas for postmenopausal women, both tamoxifen and aromatase inhibitors are acceptable treatment options. Analyses of thousands of women treated with 5 years of tamoxifen versus no endocrine therapy for invasive breast cancer have demonstrated a 31% decrease in annual breast cancer death rate (7).

An additional 60,000 women are diagnosed with non-invasive breast cancer (6), and many will be offered tamoxifen to reduce the risk of an in-breast recurrence or a new primary tumor. Moreover, well-validated, population based models have been developed to estimate an unaffected woman's risk of developing breast cancer. Women at risk for breast cancer may be recommended for therapy with tamoxifen or raloxifene (8). Several prospective randomized controlled trials have demonstrated that tamoxifen decreases the risk of a new primary breast cancer in high risk women by 40-50% (8). Thus, a substantial number of women with an increased risk for breast cancer are treated annually with anti-estrogen therapy.

Tamoxifen has both anti-estrogenic and estrogenic activity, depending upon the target organ. These differential effects lead to clinical benefit as well as to potentially bothersome side effects and rare but severe toxicity (9). Tamoxifen is anti-estrogenic in the breast, resulting in decreased breast cancer development and recurrence, as well as in the brain, leading to hot flashes. Conversely, tamoxifen is estrogenic in the bone, liver, and uterus, resulting in improvements in bone density and lipid profile, but also potentially increasing the risk of both thromboembolic disease and uterine cancer (8,9). As described above, it is unclear if tamoxifen causes or exacerbates depression, but it was recently demonstrated to have antimanic properties in patients with bipolar disorder (10).

Treatments for Concurrent Hot Flashes and Depression

Anti-estrogen therapy for patients with breast cancer, which may induce or exacerbate depression and anxiety and which frequently causes hot flashes, has led to an intersection between clinical oncology and clinical psychiatry. Prospective randomized clinical trials have demonstrated that selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) effectively decrease vasomotor symptoms in healthy menopausal women and women with breast cancer, on or off endocrine therapy (11-16). In general, these studies have shown that most of these medications decrease hot flash frequency by about 60%, compared to a decrease of 25-35% with placebo (11,12,16). These observations have primarily been made with venlafaxine, paroxetine CR, and citalopram (11, 12,15,16). In addition to these antidepressants, the antiepileptic gabapentin has also been shown to decrease hot flashes to a similar degree (16,17). Modest improvements in hot flashes have also been reported for other SSRIs and SNRIs, including fluoxetine and sertraline (18,19).

Tamoxifen Metabolism

Tamoxifen itself is a relatively weak SERM, and is considered to be a classical pro-drug that is converted to metabolites that are notably more potent than the parent drug itself. It is primarily metabolized in the liver by the cytochrome P450 (CYP) system to a number of active metabolites, including 4-hydroxytamoxifen (4-OH tamoxifen) and 4-hydroxy-N-desmethyltamoxifen, designated endoxifen (20). Endoxifen and 4-OH tamoxifen are equipotent, and both are approximately one hundred times more active as anti-estrogens than the parent compound, tamoxifen (21). However, endoxifen is present at concentrations 5-10 fold higher than 4-OH tamoxifen in most women taking tamoxifen.

Tamoxifen is converted to endoxifen principally by a non-inducible P450 enzyme that is coded for by the most polymorphic, and most studied, gene in the cytochrome P450 system: *CYP2D6*. More than 80 different major alleles of the CYP2D6 gene have been identified, many of which confer decreased or absent CYP2D6 activity, and patients can be divided into poor, intermediate, extensive, and ultrarapid metabolizer cohorts based on their genotype. While 60% of individuals of European descent are homozygous for the active, most common allele (*1), approximately 7% are homozygous for an inactive, variant allele (*4). Other alleles, including *5, *10, and *41, also confer absent CYP2D6 activity. In one study, breast cancer patients treated with tamoxifen who were homozygous for a poor metabolizer genotype (*4/*4) had significantly lower serum concentrations of endoxifen than those with the active (*1/*1) genotype (22).

These results have led to retrospective studies evaluating the effect of CYP2D6 genotype on breast cancer outcomes. In one study, ER positive breast cancer patients homozygous for the poor metabolizer genotype and who were treated with tamoxifen monotherapy were more likely to experience recurrence of breast cancer than those patients who carried an allele coding for active enzyme (adjusted hazard ratio (HR) 1.86. p=0.089) (23). These findings were consistent with the hypothesis that homozygous *4/*4 patients did not activate tamoxifen to endoxifen, and therefore received less or no benefit from the drug. Results from subsequent studies have been mixed; some confirmed this finding (24-26), while others did not (Table 1) (27,28). In fact, 2 of these studies suggested just the opposite effect: CYP2D6 *4/*4 patients actually had better outcomes when treated with monotherapy tamoxifen (27,28). Regardless, although further studies are required, these investigations suggest an important role for CYP2D6 activity in tamoxifen metabolism.

Coadministration of SSRIs/SNRIs and Tamoxifen

In addition to genetic inactivation of *CYP2D6*, CYP2D6 activity can be decreased by medications that inhibit the enzyme (22,29,30). Therefore, use of CYP2D6 inhibitors in patients who are being treated with tamoxifen, even if they have the homozygous active genotype, could potentially affect breast cancer outcomes, in a manner similar to the poor metabolizer genotype. Inhibition of tamoxifen conversion to the active metabolite endoxifen may result in decreased efficacy of tamoxifen therapy and increased risk of breast cancer development or recurrence. Several but not all SSRIs and SNRIs are potent, moderate, or mild inhibitors of CYP2D6 (Table 2).

Indeed, we have shown that women with wild-type CYP2D6 genotype treated with tamoxifen demonstrated statistically significant decreases in endoxifen concentration following initiation of concomitant paroxetine therapy (20). A subsequent observational study of women treated with tamoxifen demonstrated low serum concentrations of endoxifen in women concomitantly treated with strong inhibitors of CYP2D6 such as paroxetine and fluoxetine, and intermediate levels of endoxifen in women concomitantly treated with weak inhibitors, such as sertraline and citalopram (29). It is noteworthy that venlafaxine, which does not inhibit CYP2D6, had

little effect on endoxifen concentration. Similarly, it would be expected that other SSRIs and SNRIs that have not been shown to inhibit CYP2D6 activity, such as fluvoxamine and escitalopram, would have little effect on endoxifen concentration, although this hypothesis has not yet been formally studied.

The influence of concomitant medications in addition to CYP2D6 genotype on breast cancer outcome has also been investigated in one of the retrospective patient cohorts described above (31). Information about concomitant treatment with CYP2D6 inhibitors was extracted from the medical record and combined with genotype information to classify patients based on metabolizer status. Those women with decreased CYP2D6 metabolism had increased rates of breast cancer recurrence and decreased relapse free survival. Since it was a retrospective analysis of a previously conducted study, endoxifen concentrations were not available. Nonetheless, the authors concluded that based on these data, CYP2D6 inhibitors should probably be avoided in patients being treated with tamoxifen.

Although these studies are small relative to major studies of breast cancer outcome, the data suggest that SSRIs and SNRIs with no or minimal effect on CYP2D6 activity, such as citalopram and venlafaxine, are unlikely to interfere with the formation of endoxifen. Similarly, the anticonvulsant gabapentin is not known to affect CYP2D6 activity or the formation of endoxifen. Other SSRIs that inhibit CYP2D6 may prevent endoxifen formation and adversely affect tamoxifen activity. However, since SSRIs and SNRIs have been demonstrated to decrease hot flashes in otherwise healthy postmenopausal women who are not taking tamoxifen, and since citalopram, venlafaxine and gabapentin are as effective in reducing hot flashes as strong CYP2D6 inhibitors in women taking tamoxifen, the mechanism by which these antidepressants reduce hot flashes is likely not due to blockade of endoxifen production. Taken together, these data suggest that concomitant use of potent CYP2D6 inhibitors (see table 2) should be avoided if possible in women taking tamoxifen, unless a) patients are committed to these drugs as effective antidepressants in settings where other medications have been ineffective, or b) alternative agents, such as venlafaxine, citalopram, or gabapentin, cannot be tolerated in a patient requiring antidepressant therapy. Antidepressant therapy with escitalopram or fluvoxamine could also be considered in tamoxifen-treated patients, but the effect of these medications on hot flashes has not yet been assessed.

Clinical Implications

The retrospective data regarding CYP2D6 genotype and breast cancer outcomes in tamoxifen-treated patients were presented to the United States Food and Drug Administration at an advisory committee meeting in October 2006. At that time, some members of the panel recommended routine CYP2D6 genotyping for patients being treated with tamoxifen. However, others were more conservative given the mixed results described above (Table 1), and recommended that genotyping be considered as an option in these patients. At this time, the FDA has not changed the package insert for tamoxifen to describe metabolism by CYP2D6, or to recommend CYP2D6 genotyping of patients prior to initiation of therapy, and genotyping for CYP2D6 is not yet routinely performed in the clinical management of breast cancer patients. Further studies of the impact of CYP2D6 genotype on breast cancer outcomes are ongoing, so additional information should be available in the near future to help guide treatment decision making for individual patients (32).

At present, however, since the data suggest that CYP2D6 activity may adversely affect tamoxifen metabolism, which in turn may influence breast cancer outcomes, it is reasonable to avoid known CYP2D6 inhibitors in women taking tamoxifen assuming acceptable alternative treatment options, such as citalopram, gabapentin, or venlafaxine (see Table 2). Some women are stable on SSRI/SNRI therapy that inhibits CYP2D6, or are unable to tolerate

the medications that do not inhibit CYP2D6. In these situations, the patient's psychiatrist should discuss therapy options with the treating oncologist, since there may be alternative endocrine therapy options available for management of the patient's breast cancer. For example, ovarian suppression can be used for treatment of premenopausal women, whereas aromatase inhibitor therapy can be an excellent option for women who are postmenopausal.

In the vignette, Mrs. B was interested in taking a single medication that could treat both her depressive symptoms and her hot flashes, and she had heard that some antidepressants were able to manage both symptoms. She had previously tolerated fluoxetine without difficulty, and therefore she requested to restart this medication. Her psychiatrist had heard about the possible drug-drug interactions between tamoxifen and some SSRIs, however, and therefore she encouraged Mrs B to consider trying a different antidepressant to avoid any potential decrease in tamoxifen efficacy. The psychiatrist initiated therapy with venlafaxine XR and Mrs. B is currently taking 75 mg daily. Her depressive symptoms have improved, and her hot flashes are now mild and infrequent.

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Table 1

Summary of associations between CYP2D6 genotype and breast cancer outcome. DFS: disease-free survival; EFS: event-free survival; HR: hazard ratio; PFS: progression-free survival; RFS: relapse-free survival; TTP: time to progression; wt: wild-type. *4, *5, *10, and *41 are non-functional CYP2D6 alleles.

Study	# patients (treatment setting)	Took 2D6 inhibitors into account?	Comparison	HR	P value
Goetz (23)	223 (adjuvant)	No	*4/*4 vs wt/*4 and wt/wt	DFS 1.86	0.089
Goetz (31)	190 (adjuvant)	Yes	Decreased vs Increased	RFS 1.74	0.034
Lim (25)	202 (metastatic)	No	*10/*10 vs others	TTP 5 mo vs 21.8 mo	0.0032
Nowell (26)	162 (adjuvant)	No	wt/*4 and *4/*4 vs wt/wt	PFS 0.67	0.19
Schroth (24)	206 (adjuvant)	No	Nonfunctional allele carriers (*4, *5, *10, *41) vs wt	EFS 1.89	0.02
Wegman (28)	110 (adjuvant)	No	wt/*4 and *4/*4 vs wt/wt	RFS 0.33	0.14

Table 2

Effect of SSRIs/SNRIs and gabapentin on CYP2D6 activity (taken from www.drug-interactions.com) and on hot flashes.

Strong CYP2D6 Inhibitors		Efficacy vs placebo for hot flashes	References
Fluoxetine	Prozac®, Sarafem®	50% vs 36%, p=0.02	(18,30)
Paroxetine	Paxil®, Pexeva®	62% vs 37%, p=0.007	(12,20,30)
Moderate CYP2D6 Inhibitors			
Duloxetine	Cymbalta®	Not assessed in placebo-controlled trial	(33)
Medications That Inhibit CYP2D6 Weakly or Not at All			
Citalopram	Celexa®	49% vs 23%, p=0.0021	(15,30)
Escitalopram	Lexapro®	Not assessed in placebo-controlled trial	(34)
Fluvoxamine	Luvox®	Not assessed in placebo-controlled trial	(35)
Gabapentin	Neurontin®	46% vs 15%, p=0.007	(17)
Sertraline	Zoloft®	36% vs 27%, p=0.03	(19,30)
Venlafaxine	Effexor®	60% vs 27%, p<0.0001	(11,22,29)