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A Model Citizen? Is Tamoxifen More Effective Than Aromatase Inhibitors if We Pick the Right Patients?

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After decades of empiricism, the treatment of cancer is widely felt to be entering the era of "targeted" therapy and leading to personalized strategies for individuals with this dreaded disease. Of course, the approach to targeted therapy in oncology is not a new one. Students of breast cancer history point to Sir George Beatson's report in 1896 of the clinical improvement he observed in three young women with locally advanced breast cancer following surgical oophorectomy (1). Subsequent landmark studies by Jensen, Lippman, and McGuire, among others, demonstrated that what Beatson had actually done was remove a specific growth factor, 17β-estradiol, from its cellular target, the estrogen receptor (ER) (2-4). Clinicians now routinely use tissue ER content to individualize antiestrogen therapy for breast cancer patients (5).

This example of personalized medicine is now joined by many others (6,7). Until recently, personalized oncologic care has been based on somatic changes in the cancer, such as the overexpression of ER or HER2/neu. However, tumor-related somatic changes may be only one side of the coin that clinicians might use to make therapeutic decisions. The other side of the coin involves the use of inherited germline differences between individual patients to predict cancer outcomes and toxic effects of specific therapies, a field that has been designated "pharmacogenetics" (8,9). Several studies [reviewed in (8,9)] have illustrated the clinical potential of determining inherited single nucleotide polymorphisms in genes that encode drug targets, transporters, and metabolizing enzymes. The latter group includes enzymes that convert the therapeutic agent to an inactive and excretable metabolite or, in some cases, that activate a prodrug to an active metabolite (8,9).

The selective ER modulator tamoxifen is considered by many experts to be one such prodrug. For example, in vitro experiments have demonstrated that tamoxifen has relatively low affinity for the ER compared with its 4-hydroxylated metabolite or estrogen itself (10). In addition, the concentration of tamoxifen required to inhibit the growth of estrogen-dependent breast cancer cells in culture is approximately two orders of magnitude higher than that of 4-hydroxy-tamoxifen (11). Together, these results supported the long-held theory that the 4-hydroxy derivative of tamoxifen is the active metabolic product of tamoxifen (12). Most of the many other tamoxifen metabolites that have been identified had been considered to be irrelevant, mainly because they are present in serum at much lower concentrations than tamoxifen. However, recent data (13) from investigators in the Consortium on Breast Cancer

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Pharmacogenomics (COBRA) have led to the rediscovery and renewed interest in one of these metabolites, 4-hydroxy-*N*-desmethyl-tamoxifen, previously designated metabolite BX. This metabolite (now known as endoxifen) has the same binding affinity for ER and antiproliferative effect on cultured human breast cancer cells as 4-hydroxy-tamoxifen but is present at 5- to 10-fold higher concentrations in the serum of most women taking tamoxifen (13).

Endoxifen is generated from tamoxifen by the enzymatic activity of the product of a P450 gene, cytochrome 2D6 (*CYP2D6*) (14). Although 60% of individuals of European descent are homozygous for the active allele of *CYP2D6* (ie, the **1* allele, designated "wild type"), approximately 7% are homozygous for an inactive allele (**4* is the most common variant allele among individuals of European descent, whereas **10* is the most common allele among those of Asian descent) (15). Individuals who are homozygous for these variant *CYP2D6* alleles are poor metabolizers of substrates for the enzyme. Studies by COBRA investigators have shown that among women who take tamoxifen, those who are homozygous for inactive *CYP2D6* alleles have substantially lower endoxifen levels than those who are homozygous for the wild-type allele (14,16). Furthermore, certain concomitant medications that partially or completely block the activity of the CYP2D6 enzyme likewise result in very low serum concentrations of endoxifen (17).

What are the clinical implications of these findings? COBRA investigators have previously demonstrated 100% concordance of *CYP2D6* genotyping results between germline DNA from leukocytes and DNA extracted from formalin-fixed, paraffin-embedded (FFPE) cancer tissue (18). This technological breakthrough permits interrogation of older clinical datasets in which FFPE cancer tissue specimens were collected and archived but germline DNA (ie, from leukocytes) was not. In a joint collaboration, investigators from the Mayo Clinic and COBRA retrospectively examined (19) FFPE tumor samples from a small, but prospectively conducted trial in which women with ER-positive breast cancers were randomly assigned to receive 5 years of tamoxifen with or without 1 year of fluoxymesterone (20). In this study, women with homozygous variant *CYP2D6* who received adjuvant tamoxifen alone had higher rates of recurrence than those with the wild-type genotype, and the authors concluded that perhaps this poorer outcome was a result of poor conversion of tamoxifen to endoxifen. This effect was echoed by the use of CYP2D6 inhibitors in women who were wild type for *CYP2D6* (21).

Several subsequent investigations have addressed the interaction between *CYP2D6* genotype and outcomes in women who were treated with tamoxifen in the prevention (22), adjuvant (23–27), and metastatic (28) settings. The results of two of the adjuvant studies (26,27), as well as the metastatic trial (28) and the prevention study (22), are consistent with the hypothesis that women with variant *CYP2D6* genotype do not activate tamoxifen and therefore have worse outcomes. However, the other three adjuvant studies (22-24) failed to support this theory, and remarkably, two studies (24,25) provided statistically significant evidence of exactly the opposite effect: that women with homozygous *CYP2D6* variants have better outcomes than those who are wild type when treated with tamoxifen. Although disconcerting, these disparate conclusions are not unexpected when one considers that these studies are small and mostly retrospective and that they address different treatment settings and are confounded by different doses and durations of tamoxifen therapy, patient selection, and the effects of other drugs and tumor-related somatic changes, all of which may affect the activity of tamoxifen. Because metabolism of tamoxifen is quite complex, it is also likely that inactivating *CYP2D6* alleles other than **4*, and indeed germline differences in completely different genes, each of which have been only superficially examined, may also play a role in the activity of this agent (23-25).

One must ask if these pharmacogenetic findings for tamoxifen are relevant today for women with ER-positive breast cancer. Even if poor metabolizers do have a worse prognosis when

treated with tamoxifen monotherapy, we must consider whether this agent has become a clinically irrelevant historical bookmark. Several studies (29-33) have now shown that for postmenopausal women with ER-positive breast cancer, estrogen depletion with an aromatase inhibitor is generally more effective than tamoxifen in both the adjuvant and metastatic settings. A panel convened by the American Society of Clinical Oncology has recommended the use of an aromatase inhibitor at some time in the course of treatment for all postmenopausal women with ER-positive breast cancer (34). However, despite this enthusiastic endorsement, aromatase inhibitors are not ideal for all women because they are associated with substantially more common and often more severe musculoskeletal complaints that often lead to nonadherence (35,36), as well as with higher long-term risks for osteoporosis and fractures (30,37,38). Moreover, because aromatase inhibitors are contraindicated in premenopausal women, tamoxifen is currently the treatment of choice for these patients. Tamoxifen and the related selective ER modulator raloxifene are approved for chemoprevention, whereas aromatase inhibitors are not. Finally, tamoxifen is also effective in the metastatic setting, and as more women receive adjuvant aromatase inhibitor therapy, those who do relapse will be treated with tamoxifen. Therefore, in the foreseeable future, most premenopausal women and many postmenopausal women at risk for or with ER-positive breast cancer may consider tamoxifen at some point in their treatment.

In this issue of the Journal, Punglia et al. (39) have used assumptions drawn from the Mayo–COBRA study (19,21) to build a model to estimate whether women with wild-type CYP2D6 might have superior outcomes if they take tamoxifen rather than an aromatase inhibitor. Applying this model to results produced from the Breast International Group 1-98 trial, one of the large prospective randomized clinical trials to compare tamoxifen with the aromatase inhibitor letrozole (30), they conclude that women who have the wild-type *CYP2D6* genotype would actually have lower rates of relapse when treated with tamoxifen. If this model is correct, the role of *CYP2D6* genotype testing would be critical for selecting the optimal adjuvant endocrine treatment for women with ER-positive breast cancer because it implies that more than 90% of women (those who are wild type for *CYP2D6*) would actually have better outcomes if they received tamoxifen instead of an aromatase inhibitor and that those who are homozygous for inactivating variant alleles should take an aromatase inhibitor.

Is this model applicable to the real world, and should *CYP2D6* genotype testing be incorporated into routine care at this time? The conclusions reached by Punglia et al. (39) depend on the estimated hazard rates for recurrence for women taking tamoxifen and are based on the relative effects of CYP2D6-mediated conversion of tamoxifen to endoxifen. These estimated hazard rates were based on data from the single study from the Mayo–COBRA collaboration (19) and ignore the considerable heterogeneity of outcomes of tamoxifen-treated women when analyzed by the effects of *CYP2D6* genotypes reported in the numerous other studies, discussed above. Because of this uncertainty, and despite the Punglia et al. model, we do not recommend routine *CYP2D6* genotyping for all patients who are considering tamoxifen, although we recognize that there are already selected circumstances in which such knowledge might be helpful. At the least, however, women who are taking tamoxifen should avoid the concomitant use of drugs that inhibit CYP2D6 activity if possible. Ironically, some of the most potent inhibitors of CYP2D6 are the selective serotonin uptake inhibitors and the selective serotonin norepinephrine inhibitors (SSNRIs), which are frequently used for treatment of hot flashes (40). Examples of these inhibitors include paroxetine and fluoxetine. However, other SSNRIs, such as venlafaxine, do not inhibit CYP2D6 yet are quite effective for treatment of hot flashes, and as such would be the preferred treatment for these patients (17,41).

Regardless, we believe that these studies have brought the field of pharmacogenetics onto the radar screen of clinicians caring for breast cancer patients. The model reported by Punglia et al. (39) suggests that selection of endocrine therapy based on *CYP2D6* genotype might make

tamoxifen more than just another choice, but actually the preferred choice, for women with ER-positive breast cancer who are wild type for the *CYP2D6* gene. However, as with all tumor marker research, early studies are often quite positive, and rigorous validation of these results is critical before widespread adoption (42,43). Ongoing and planned studies of archived FFPE specimens from the large randomized trials that have compared tamoxifen with an aromatase inhibitor should provide definitive experimental data regarding inherited differences in *CYP2D6* and other genes that should confirm or refute the hypothesis that *CYP2D6* genotype might be used to effectively guide endocrine therapy for women with ER-positive breast cancer.

The future of personalized cancer medicine will likely use both sides of the coin by incorporating both tumor-related somatic changes and inherited germline pharmacogenetic factors to predict the best course of treatment for a specific patient. Alone, each may have limited value, but the whole is likely to be greater than the sum of the parts. These exciting findings highlight the importance of prospective collection, processing, and storage of biospecimens for future studies of yet-undiscovered somatic and germline markers to permit studies of individualized treatments. Increasingly, biologic subgroup analyses from large clinical trials have become as or more interesting than the overall results. We encourage all investigators, both public and private, to be certain that tissue and germline (leukocytes or buccal swabs) specimens are collected and made available for such translational research (44).

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References

1. Beatson GW. On the treatment of inoperable cases of carcinoma of the mamma: suggestions for a new method of treatment with illustrative cases. Lancet 1896;148(3802):104–107.
2. Jensen EV. Estrogen receptors in hormone-dependent breast cancers. Cancer Res 1975;35(11 pt 2): 3362–3364. [PubMed: 172222]
3. McGuire WL. Current status of estrogen receptors in human breast cancer. Cancer 1975;36(2):638–644. [PubMed: 168960]
4. Lippman ME, Bolan G. Oestrogen-responsive human breast cancer in long term tissue culture. Nature 1975;256(5518):592–593. [PubMed: 170527]
5. Early Breast Cancer Trialists' Collaborative Group. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005;365(9472):1687–1717. [PubMed: 15894097]
6. Harris L, Fritsche H, Mennel R, et al. American Society of Clinical Oncology 2007 update of recommendations for the use of tumor markers in breast cancer. J Clin Oncol 2007;25(33):5287–5312. [PubMed: 17954709]
7. Wolff AC, Hammond ME, Schwartz JN, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. J Clin Oncol 2007;25(1):118–145. [PubMed: 17159189]
8. Weinshilboum R. Inheritance and drug response. N Engl J Med 2003;348(6):529–537. [PubMed: 12571261]
9. Evans WE, McLeod HL. Pharmacogenomics—drug disposition, drug targets, and side effects. N Engl J Med 2003;348(6):538–549. [PubMed: 12571262]
10. Wakeling AE, Slater SR. Estrogen-receptor binding and biologic activity of tamoxifen and its metabolites. Cancer Treat Rep 1980;64(6–7):741–744. [PubMed: 7427959]

11. Marth C, Daxenbichler G, Buehring GC, Hofstadter F, Dapunt O. Inhibition of the estradiol-induced growth of cultured human breast cancer cells by the anti-estrogens tamoxifen, desmethyl-tamoxifen, 4-hydroxy-tamoxifen and enclomiphene. Biochem Pharmacol 1984;33(24):3951–3956. [PubMed: 6439216]
12. Osborne CK. Tamoxifen in the treatment of breast cancer. N Engl J Med 1998;339(22):1609–1618. [PubMed: 9828250]
13. Johnson MD, Zuo H, Lee KH, et al. Pharmacological characterization of 4-hydroxy-N-desmethyl tamoxifen, a novel active metabolite of tamoxifen. Breast Cancer Res Treat 2004;85(2):151–159. [PubMed: 15111773]
14. Stearns V, Johnson MD, Rae JM, et al. Active tamoxifen metabolite plasma concentrations after coadministration of tamoxifen and the selective serotonin reuptake inhibitor paroxetine. J Natl Cancer Inst 2003;95(23):1758–1764. [PubMed: 14652237]
15. Garte S, Gaspari L, Alexandrie AK, et al. Metabolic gene polymorphism frequencies in control populations. Cancer Epidemiol Biomarkers Prev 2001;10(12):1239–1248. [PubMed: 11751440]
16. Borges S, Desta Z, Li L, et al. Quantitative effect of CYP2D6 genotype and inhibitors on tamoxifen metabolism: implication for optimization of breast cancer treatment. Clin Pharmacol Ther 2006;80 (1):61–74. [PubMed: 16815318]
17. Jin Y, Desta Z, Stearns V, et al. CYP2D6 genotype, antidepressant use, and tamoxifen metabolism during adjuvant breast cancer treatment. J Natl Cancer Inst 2005;97(1):30–39. [PubMed: 15632378]
18. Rae JM, Cordero KE, Scheys JO, Lippman ME, Flockhart DA, Johnson M. Genotyping for polymorphic drug metabolizing enzymes from paraffin-embedded and immunohistochemically stained tumor samples. Pharmacogenetics 2003;13(8):501–507. [PubMed: 12893988]
19. Goetz MP, Rae JM, Suman VJ, et al. Pharmacogenetics of tamoxifen bio-transformation is associated with clinical outcomes of efficacy and hot flashes. J Clin Oncol 2005;23(36):9312–9318. [PubMed: 16361630]
20. Ingle JN, Twito DI, Schaid DJ, et al. Combination hormonal therapy with tamoxifen plus fluoxymesterone versus tamoxifen alone in postmenopausal women with metastatic breast cancer. An updated analysis. Cancer 1991;67(4):886–891. [PubMed: 1991261]
21. Goetz MP, Knox SK, Suman VJ, et al. The impact of cytochrome P450 2D6 metabolism in women receiving adjuvant tamoxifen. Breast Cancer Res Treat 2007;101(1):113–121. [PubMed: 17115111]
22. Bonanni B, Macis D, Maisonneuve P, et al. Polymorphism in the CYP2D6 tamoxifen-metabolizing gene influences clinical effect but not hot flashes: data from the Italian Tamoxifen Trial. J Clin Oncol 2006;24(22):3708–3709. [PubMed: 16877740]author reply 3709
23. Nowell SA, Ahn J, Rae JM, et al. Association of genetic variation in tamoxifen-metabolizing enzymes with overall survival and recurrence of disease in breast cancer patients. Breast Cancer Res Treat 2005;91(3):249–258. [PubMed: 15952058]
24. Wegman P, Elingarami S, Carstensen J, Stal O, Nordenskjold B, Wingren S. Genetic variants of CYP3A5, CYP2D6, SULT1A1, UGT2B15 and tamoxifen response in postmenopausal patients with breast cancer. Breast Cancer Res 2007;9(1):R7. [PubMed: 17244352]
25. Wegman P, Vainikka L, Stal O, et al. Genotype of metabolic enzymes and the benefit of tamoxifen in postmenopausal breast cancer patients. Breast Cancer Res 2005;7(3):R284–R290. [PubMed: 15987423]
26. Schroth W, Antoniadou L, Fritz P, et al. Breast cancer treatment outcome with adjuvant tamoxifen relative to patient CYP2D6 and CYP2C19 genotypes. J Clin Oncol 2007;25(33):5187–5193. [PubMed: 18024866]
27. Kiyotani K, Mushiroda T, Sasa M, et al. Impact of CYP2D6*10 on recurrence-free survival in breast cancer patients receiving adjuvant tamoxifen therapy. Cancer Sci 2008;99(5):995–999. [PubMed: 18294285]
28. Lim HS, Ju Lee H, Seok Lee K, Sook Lee E, Jang IJ, Ro J. Clinical implications of CYP2D6 genotypes predictive of tamoxifen pharmacokinetics in metastatic breast cancer. J Clin Oncol 2007;25(25): 3837–3845. [PubMed: 17761971]
29. Howell A, Cuzick J, Baum M, et al. Results of the ATAC(Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. Lancet 2005;365 (9453):60–62. [PubMed: 15639680]

30. Thurlimann B, Keshaviah A, Coates AS, et al. A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer. N Engl J Med 2005;353(26):2747–2757. [PubMed: 16382061]

31. Coombes RC, Hall E, Gibson LJ, et al. A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. N Engl J Med 2004;350 (11):1081–1092. [PubMed: 15014181]

32. Jakesz R, Greil R, Gnant M, et al. Extended adjuvant therapy with anastrozole among postmenopausal breast cancer patients: results from the randomized Austrian Breast and Colorectal Cancer Study Group Trial 6a. J Natl Cancer Inst 2007;99(24):1845–1853. [PubMed: 18073378]

33. Mauri D, Pavlidis N, Polyzos NP, Ioannidis JP. Survival with aromatase inhibitors and inactivators versus standard hormonal therapy in advanced breast cancer: meta-analysis. J Natl Cancer Inst 2006;98(18):1285–1291. [PubMed: 16985247]

34. Winer EP, Hudis C, Burstein HJ, et al. American Society of Clinical Oncology technology assessment on the use of aromatase inhibitors as adjuvant therapy for postmenopausal women with hormone receptor-positive breast cancer: status report 2004. J Clin Oncol 2005;23(3):619–629. [PubMed: 15545664]

35. Henry NL, Giles JT, Ang D, et al. Prospective characterization of musculoskeletal symptoms in early stage breast cancer patients treated with aromatase inhibitors. Breast Cancer Res Treat. 2007[e-published ahead of print]

36. Crew KD, Greenlee H, Capodice J, et al. Prevalence of joint symptoms in postmenopausal women taking aromatase inhibitors for early-stage breast cancer. J Clin Oncol 2007;25(25):3877–3883. [PubMed: 17761973]

37. Buzdar A, Howell A, Cuzick J, et al. Comprehensive side-effect profile of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: long-term safety analysis of the ATAC trial. Lancet Oncol 2006;7(8):633–643. [PubMed: 16887480]

38. Coombes RC, Bliss JM, Hall E. Safety of exemestane in the Intergroup Exemestane Study. J Clin Oncol 2005;23(13):3171–3172. [PubMed: 15860896]

39. Punglia RS, Burstein HJ, Winer EP, Weeks JC. Pharmacogenomic variation of *CYP2D6* and the choice of optimal adjuvant endocrine therapy for postmenopausal breast cancer: a modeling analysis. J Natl Cancer Inst 2008;100(9):642–648. [PubMed: 18445827]

40. Stearns V, Ullmer L, Lopez JF, Smith Y, Isaacs C, Hayes D. Hot flushes. Lancet 2002;360(9348): 1851–1861. [PubMed: 12480376]

41. Loprinzi CL, Kugler JW, Sloan JA, et al. Venlafaxine in management of hot flashes in survivors of breast cancer: a randomised controlled trial. Lancet 2000;356(9247):2059–2063. [PubMed: 11145492]

42. Ransohoff DF. Rules of evidence for cancer molecular-marker discovery and validation. Nat Rev Cancer 2004;4(4):309–314. [PubMed: 15057290]

43. Hayes DF, Bast R, Desch CE, et al. A tumor marker utility grading system (TMUGS): a framework to evaluate clinical utility of tumor markers. J Natl Cancer Inst 1996;88(20):1456–1466. [PubMed: 8841020]

44. Dowsett M, Goldhirsch A, Hayes DF, Senn HJ, Wood W, Viale G. International web-based consultation on priorities for translational breast cancer research. Breast Cancer Res 2007;9(6):R81. [PubMed: 18034879]