editorials

Pharmacogenomics and Endocrine Therapy in Breast Cancer

Daniel F. Hayes, MD[1] and James M. Rae, PhD[2]

In 1896, Sir George Beatson reported that removal of the ovaries from three young women with locally advanced breast cancer resulted in substantial tumor shrinkage.[1] Beatson's report set the stage for what is arguably the anticancer treatment with the most impact in regards to lives saved: endocrine therapy (ET) for breast cancer.[2] Nonetheless, ET is far from 100% effective, which raises the question, Why doesn't ET work for all patients? McGuire and colleagues[3] first reported that estrogen receptor (ER) is a very potent predictive factor for ET, and subsequent studies have demonstrated that ER-negative cancers are completely refractory to ET.[2] Since then, investigators have focused principally on identifying acquired somatic tumor alterations in ER-positive cancers that might confer resistance to ET, including upregulation of alternative pathways such as human epidermal growth factor 2 (HER2)[4] or the appearance of mutations in *ESR1* (the gene that encodes for ER[5]) or in *PIK3CA*.[6]

Inherited germline pharmacogenetic differences might also explain the variable responses to ET. Of these, the pharmacogenomics of tamoxifen have been the most widely studied. Tamoxifen competes with estrogen for ER binding and induces cellular responses. The effects of tamoxifen are tissue specific, exhibiting ER antagonism in breast and brain but ER agonism in bone, liver, and uterus.[7] These differential effects have led to the designation of tamoxifen as a selective ER modulator (SERM) rather than an antiestrogen.

Tamoxifen is, in part, considered a prodrug, because the parent compound binds to ER with a much lower (approximately 100-fold) affinity than two of its more potent active metabolites, 4-hydroxy tamoxifen and 4-hydroxy, N-desmethyl tamoxifen, also designated endoxifen.[8] Each of these metabolites exhibits much higher ER antagonism than the parent drug. In women taking 20 mg per day, parent tamoxifen is present at approximately 100 times the concentration of 4-hydroxy tamoxifen, which is produced through a number of enzymatic and redundant steps in the liver. Likewise, in most patients, endoxifen levels are approximately sixfold higher than those of 4-hydroxy tamoxifen, although still significantly lower than tamoxifen levels.[9]

The metabolism of tamoxifen to endoxifen depends almost exclusively on the activity of a single hepatic enzyme, CYP2D6. Pharmacogeneticists have long recognized the variable metabolism of several drugs based on *CYP2D6* genotypes, which separate patients into four metabolic phenotypes: poor, intermediate, extensive, and ultrarapid.[10] Nearly 20 years ago, the Consortium of Breast Cancer Pharmacogenomics reported that patients with homozygous deleterious single nucleotide polymorphisms in the gene encoding CYP2D6, and who are therefore considered poor metabolizers, have six-fold to 10-fold lower circulating endoxifen levels compared with those with wild-type *CYP2D6* genotype (extensive metabolizers).[11]

The observation that endoxifen levels are associated with a *CYP2D6* genotype raised the hypothesis that extensive metabolizers, who are expected to have higher levels of endoxifen, might have a better outcome when treated with tamoxifen than those who inherit a poor metabolic genotype.[9] An initial pilot study supported this theory,[12] and subsequently more than 70 publications have addressed this issue.[13,14] Indeed, some of them seem to have validated these findings,[15] whereas others have reported no difference in outcomes in women taking tamoxifen according to genotype.[16,17] At least one study had inexplicable results: it reported better outcomes in those who would be expected to be poor metabolizers.[18] Indeed, in light of these highly disparate results, we urged caution against using *CYP2D6* genotype to guide ET for women with ER-positive breast cancer, pending more conclusive evidence.[19]

The confusion surrounding *CYP2D6* genotype as a biomarker for tamoxifen activity highlights many of the issues surrounding tumor biomarker test studies and the need to rigorously demonstrate analytical validity and clinical utility.[20] The analytical validity of the tests used to determine *CYP2D6* genotype has been controversial. In the original and several other studies, DNA for genotyping was derived from somatic tumor tissue.[12] However, other investigators have used germline tissue (leukocytes or mucosal fibroblasts) for genotyping, arguing that this analytical approach is more accurate.[21] Subsequent studies have demonstrated that the *CYP2D6* genotype results obtained by comparing germline specimens with tumor specimens are nearly identical, putting this argument to rest.[22-26]

A second reason for the diverse conclusions reached in the many studies on this topic requires a clear

ASSOCIATED CONTENT

See accompanying articles on pages 548 and 558

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on December 2, 2019 and published at ascopubs.org/journal/jco on December 27, 2019: DOI https://doi.org/10.1200/JCO.19.03119

understanding of the biology of the ER signaling pathway and tamoxifen metabolism. Although tamoxifen is a weaker SERM than either 4-hydroxy tamoxifen or endoxifen, nonetheless, it has ER antagonistic activity and is present in much higher concentrations in the blood stream, as are two other major metabolites with antagonist activity, desmethyl-tamoxifen and didesmethyl-tamoxifen.[27] Furthermore, although 4-hydroxy tamoxifen is present in much lower levels than tamoxifen or endoxifen, it has very high affinity for ER. Finally, although endoxifen levels are much reduced in patients who are poor *CYP2D6* metabolizers, this metabolite is still present in such patients, albeit at low concentrations.[9] Taken together, these factors suggest that it is very likely that tumor levels of ER are saturated regardless of whether the parent drug is rapidly or poorly converted to endoxifen.[27]

A third explanation is related to study design and conduct.[28] The majority of studies that have contributed to the tamoxifen/CYP2D6 controversy, unfortunately, are studies of convenience confounded by several factors.[29] There have been only a few studies that were prospectively conducted using specimens previously collected and archived within clinical trials of ET (so-called prospective-retrospective studies[30]), and two of the largest of these failed to show any association between *CYP2D6* genotype and breast cancer outcomes.[16,17]

In this issue of *Journal of Clinical Oncology*, two new studies are reported that may further inform this debate. By retrospectively gleaning data from two Swedish breast cancer cohort registries linked to the Swedish Prescribed Drug Registry, He et al[31] identified and genotyped more than 1,300 patients assigned to take adjuvant tamoxifen. They found that discontinuation rates, presumably because of toxicity, were 7.2%, 7.6%, 6.7%, and 18.8% among poor, intermediate, normal, and ultrarapid *CYP2D6* metabolizers, respectively, confirming previously published reports.[32-34]

They observed a U-shaped association for breast cancer–specific mortality, with highest rates in the poor and ultrarapid metabolizer groups, which is rather difficult to explain. The authors speculate that the worse outcomes in the poor metabolizers are consistent with the overall hypothesis that endoxifen is the primary modulator of tamoxifen efficacy, and that the worse outcomes in the ultrarapid metabolizers were a result of early discontinuation of tamoxifen secondary to higher toxicity rates. However, we argue that the poor outcomes observed in the slow metabolizers may be confounded by a variety of factors in this retrospective outcomes registry study. With respect to toxicity, in modern practice, if tamoxifen seems to be the initial treatment of choice, the clinician can easily initiate it without regard to *CYP2D6* genotype. If the patient is intolerant, the patient can be switched to an aromatase inhibitor.

In a second article, Tamura et al[35] report the results of a prospective randomized clinical trial of 136 Japanese patients with stage IV or recurrent ER-positive breast cancer who had heterozygous or homozygous nonfunctional variant *CYP2D6* genotypes, and thus were expected to be poor or intermediate metabolizers. They were randomly assigned to receive tamoxifen at the standard dose (20 mg/day) or an increased dose (40 mg/day). As expected, for patients treated with the higher dose compared with the lower dose, serum trough levels of endoxifen were substantially and significantly increased and were even higher than those in a control group of patients who were extensive *CYP2D6* metabolizers. Nonetheless, progression-free survival rates at 6 months (the primary end point) were the same for the patients randomly assigned to standard-dose versus high-dose tamoxifen (66.7% *v* 67.6%, respectively).

At least three other prospective clinical trials have been performed to test the test, which is considered the gold standard for establishing the clinical utility of a tumor biomarker test.[36,37] Sanchez-Spitman et al[38] found no association between endoxifen concentrations or *CYP2D6* genotype and relapse-free survival in 667 pre- and postmenopausal patients taking adjuvant tamoxifen. Likewise, Neven et al[39] found that neither objective response rates (the primary end point of their trial), nor clinical benefit, nor progression-free survival were related to endoxifen levels in 247 evaluable patients with ER-positive breast cancer in neoadjuvant or metastatic settings. Love et al[40] reported an incongruous result in a cohort of 224 Filipino and Vietnamese patients: the risk of recurrence was higher rather than lower for those who were CYP2D6 extensive metabolizers with high endoxifen concentrations.

What should we make of these results? In our opinion, which is consistent with the most recent versions of the American Society of Clinical Oncology and the National Comprehensive Cancer Network Practice Guidelines,[41,42] *CYP2D6* genotype should not be used to guide ET for women with ER-positive early or metastatic breast cancer. Any tumor biomarker test should be introduced into clinical practice only when it is shown with high levels of evidence to have clinical utility. The confounding results of the He et al[31] study are insufficient to be a conclusive validation of the hypothesis. The prospective nature of the Tamura et al[35] study provides more high-level evidence that CP2D6 status does not affect the efficacy of tamoxifen in patients with ER-positive breast cancer.

AFFILIATIONS

[1]University of Michigan Rogel Cancer Center, Ann Arbor, MI
[2]University of Michigan Medical School, Ann Arbor, MI

CORRESPONDING AUTHOR

Daniel F. Hayes, MD, University of Michigan Rogel Cancer Center, CCC6312, 1500 E. Medical Center Dr, Ann Arbor MI 48109-5942; e-mail: hayesdf@umich.edu.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.1200/JCO.19.03119.

REFERENCES

1. Beatson GT: On the treatment of inoperable cases of carcinoma of the mamma: Suggestions for a new method of treatment, with illustrative cases. Trans Med Chir Soc Edinb 15:153-179, 1896
2. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Davies C, Godwin J, et al: Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: Patient-level meta-analysis of randomised trials. Lancet 378:771-784, 2011
3. McGuire WL, Chamness GC: Studies on the estrogen receptor in breast cancer. Adv Exp Med Biol 36:113-136, 1973
4. Yamauchi H, Stearns V, Hayes DF: When is a tumor marker ready for prime time? A case study of c-erbB-2 as a predictive factor in breast cancer. J Clin Oncol 19:2334-2356, 2001
5. Robinson DR, Wu YM, Vats P, et al: Activating ESR1 mutations in hormone-resistant metastatic breast cancer. Nat Genet 45:1446-1451, 2013
6. Bosch A, Li Z, Bergamaschi A, et al: PI3K inhibition results in enhanced estrogen receptor function and dependence in hormone receptor-positive breast cancer. Sci Transl Med 7:283ra51, 2015
7. Jordan C: Historical perspective on hormonal therapy of advanced breast cancer. Clin Ther 24:A3-A16, 2002
8. Lim YC, Desta Z, Flockhart DA, et al: Endoxifen (4-hydroxy-N-desmethyl-tamoxifen) has anti-estrogenic effects in breast cancer cells with potency similar to 4-hydroxy-tamoxifen. Cancer Chemother Pharmacol 55:471-478, 2005
9. 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 80:61-74, 2006
10. Hicks JK, Swen JJ, Gaedigk A: Challenges in CYP2D6 phenotype assignment from genotype data: A critical assessment and call for standardization. Curr Drug Metab 15:218-232, 2014
11. Jin Y, Desta Z, Stearns V, et al: CYP2D6 genotype, antidepressant use, and tamoxifen metabolism during adjuvant breast cancer treatment. J Natl Cancer Inst 97:30-39, 2005
12. Goetz MP, Rae JM, Suman VJ, et al: Pharmacogenetics of tamoxifen biotransformation is associated with clinical outcomes of efficacy and hot flashes. J Clin Oncol 23:9312-9318, 2005
13. Drögemöller BI, Wright GEB, Shih J, et al: CYP2D6 as a treatment decision aid for ER-positive non-metastatic breast cancer patients: A systematic review with accompanying clinical practice guidelines. Breast Cancer Res Treat 173:521-532, 2019
14. Hwang GS, Bhat R, Crutchley RD, et al: Impact of CYP2D6 polymorphisms on endoxifen concentrations and breast cancer outcomes. Pharmacogenomics J 18: 201-208, 2018
15. Brauch H, Schroth W, Goetz MP, et al: Tamoxifen use in postmenopausal breast cancer: CYP2D6 matters. J Clin Oncol 31:176-180, 2013
16. Rae JM, Drury S, Hayes DF, et al: CYP2D6 and UGT2B7 genotype and risk of recurrence in tamoxifen-treated breast cancer patients. J Natl Cancer Inst 104: 452-460, 2012
17. Regan MM, Leyland-Jones B, Bouzyk M, et al: CYP2D6 genotype and tamoxifen response in postmenopausal women with endocrine-responsive breast cancer: The Breast International Group 1-98 trial. J Natl Cancer Inst 104:441-451, 2012
18. Wegman P, Elingarami S, Carstensen J, et al: Genetic variants of CYP3A5, CYP2D6, SULT1A1, UGT2B15 and tamoxifen response in postmenopausal patients with breast cancer. Breast Cancer Res 9:R7, 2007
19. Hayes DF, Stearns V, Rae J, et al: A model citizen? Is tamoxifen more effective than aromatase inhibitors if we pick the right patients? J Natl Cancer Inst 100: 610-613, 2008
20. McShane LM, Hayes DF: Publication of tumor marker research results: The necessity for complete and transparent reporting. J Clin Oncol 30:4223-4232, 2012
21. Ratain MJ, Nakamura Y, Cox NJ: CYP2D6 genotype and tamoxifen activity: Understanding interstudy variability in methodological quality. Clin Pharmacol Ther 94:185-187, 2013
22. Rae JM, Cordero KE, Scheys JO, et al: Genotyping for polymorphic drug metabolizing enzymes from paraffin-embedded and immunohistochemically stained tumor samples. Pharmacogenetics 13:501-507, 2003
23. Hertz DL, Kidwell KM, Thibert JN, et al: Genotyping concordance in DNA extracted from formalin-fixed paraffin embedded (FFPE) breast tumor and whole blood for pharmacogenetic analyses. Mol Oncol 9:1868-1876, 2015
24. Ahern TP, Hertz DL, Damkier P, et al: Cytochrome P-450 2D6 (CYP2D6) genotype and breast cancer recurrence in tamoxifen-treated patients: Evaluating the importance of loss of heterozygosity. Am J Epidemiol 185:75-85, 2017
25. Dezentjé VO, van Schaik RH, Vletter-Bogaartz JM, et al: CYP2D6 genotype in relation to tamoxifen efficacy in a Dutch cohort of the Tamoxifen Exemestane Adjuvant Multinational (TEAM) trial. Breast Cancer Res Treat 140:363-373, 2013
26. Thompson AM, Johnson A, Quinlan P, et al: Comprehensive CYP2D6 genotype and adherence affect outcome in breast cancer patients treated with tamoxifen monotherapy. Breast Cancer Res Treat 125:279-287, 2011
27. Dowsett M, Haynes BP: Hormonal effects of aromatase inhibitors: Focus on premenopausal effects and interaction with tamoxifen. J Steroid Biochem Mol Biol 86:255-263, 2003
28. Institute of Medicine: Evolution of Translational Omics: Lessons Learned and the Path Forward. Washington, DC, The National Academies Press, 2012
29. McShane LM, Altman DG, Sauerbrei W, et al: REporting recommendations for tumor MARKer prognostic studies (REMARK). Breast Cancer Res Treat 100: 229-235, 2006
30. Simon RM, Paik S, Hayes DF: Use of archived specimens in evaluation of prognostic and predictive biomarkers. J Natl Cancer Inst 101:1446-1452, 2009
31. He W, Grassmann F, Eriksson M, et al: CYP2D6 genotype predicts tamoxifen discontinuation and prognosis in patients with breast cancer. J Clin Oncol 38: 538-547, 2020
32. Dezentjé VO, van Blijderveen NJ, Gelderblom H, et al: Effect of concomitant CYP2D6 inhibitor use and tamoxifen adherence on breast cancer recurrence in early-stage breast cancer. J Clin Oncol 28:2423-2429, 2010

33. Nardin JM, Schroth W, Almeida TA, et al: The influences of adherence to tamoxifen and CYP2D6 pharmacogenetics on plasma concentrations of the active metabolite (Z)-endoxifen in breast cancer. Clin Transl Sci 10.1111/cts.12707[epub ahead of print October 1, 2019]
34. Henry NL, Rae JM, Li L, et al: Association between CYP2D6 genotype and tamoxifen-induced hot flashes in a prospective cohort. Breast Cancer Res Treat 117: 571-575, 2009
35. Tamura K, Imamura CK, Takano T, et al: CYP2D6 genotype–guided tamoxifen dosing in hormone receptor–positive metastatic breast cancer (TARGET-1): A randomized, open-label, phase II study. J Clin Oncol 38:558-566, 2020
36. Sargent DJ, Conley BA, Allegra C, et al: Clinical trial designs for predictive marker validation in cancer treatment trials. J Clin Oncol 23:2020-2027, 2005
37. Freidlin B, McShane LM, Korn EL: Randomized clinical trials with biomarkers: Design issues. J Natl Cancer Inst 102:152-160, 2010
38. Sanchez-Spitman AB, Moes DA, Gelderblom H, et al: The effect of rs5758550 on CYP2D6*2 phenotype and formation of endoxifen in breast cancer patients using tamoxifen. Pharmacogenomics 18:1125-1132, 2017
39. Neven P, Jongen L, Lintermans A, et al: Tamoxifen metabolism and efficacy in breast cancer: A prospective multicenter trial. Clin Cancer Res 24:2312-2318, 2018
40. Love RR, Desta Z, Flockhart D, et al: CYP2D6 genotypes, endoxifen levels, and disease recurrence in 224 Filipino and Vietnamese women receiving adjuvant tamoxifen for operable breast cancer. Springerplus 2:52, 2013
41. Harris LN, Ismaila N, McShane LM, et al: Use of biomarkers to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 34:1134-1150, 2016
42. Gradishar W, Salerno KE: NCCN Guidelines Update: Breast Cancer. J Natl Compr Canc Netw 14:641-644, 2016

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Pharmacogenomics and Endocrine Therapy in Breast Cancer

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/journal/jco/site/ifc.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Daniel F. Hayes
Stock and Other Ownership Interests: Oncimmune, Inbiomotion
Consulting or Advisory Role: Cepheid, Freenome, Cellworks, CVS Caremark Breast Cancer Expert Panel, Agendia, Epic Sciences, Salutogenic Innovations
Research Funding: AstraZeneca (Inst), Pfizer (Inst), Merrimack Pharmaceuticals (Inst), Menarini Silicon Biosystems (Inst), Eli Lilly (Inst), Puma Biotechnology (Inst)
Patents, Royalties, Other Intellectual Property: Royalties from licensed technology; Diagnosis and Treatment of Breast Cancer. Patent No. US 8,790,878 B2. Date of Patent: Jul. 29, 2014. Applicant Proprietor: University of Michigan. Dr. Daniel F. Hayes is designated as inventor/co-inventor; Circulating Tumor Cell Capturing Techniques and Devices. Patent No.: US 8,951,484 B2. Date of Patent: Feb. 10, 2015. Applicant Proprietor: University of Michigan. Dr. Daniel F. Hayes is designated as inventor/co-inventor; Title: A method for predicting progression free and overall survival at each follow up timepoint during therapy of metastatic breast cancer patients using circulating tumor cells. Patent no. 05725638.0-1223-US2005008602.
Travel, Accommodations, Expenses: Menarini Silicon Biosystems
Other Relationship: Menarini Silicon Biosystems

No other potential conflicts of interest were reported.