HHS Public Access

Author manuscript

Clin Cancer Res. Author manuscript; available in PMC 2021 August 03.

Published in final edited form as:

Clin Cancer Res. 2016 December 15; 22(24): 6301. doi:10.1158/1078-0432.CCR-16-2351.

"Individualized Tamoxifen Dose Escalation"— Response

Daniel L Hertz[1], **James M Rae**[2]

[1]Department of Clinical Pharmacy, University of Michigan College of Pharmacy, Ann Arbor, MI, United States

[2]Department of Internal Medicine, Division of Hematology/Oncology, University of Michigan Medical School

We thank Koolen and colleagues for their thoughtful response to our commentary about the lack of evidence supporting tamoxifen dose escalation based on predicted or measured endoxifen concentrations (1). They state that "if the concentration has been measured and it is far below the currently adopted minimum value for efficacy of approximately 6 ng/mL, we feel it is unethical not to intervene and not trying to increase the exposure." The critical phrase in their assertion is "if the concentration has been measured," whereas in our commentary we take the position that endoxifen concentrations should not be measured given the current lack of evidence supporting this approach.

The authors posited that breast cancer patients taking tamoxifen could benefit from systemic endoxifen concentration measurements. As clinical pharmacologists, we agree that patients with lower drug concentrations may experience inferior therapeutic effectiveness; however, there is an established translational pathway for biomarker hypotheses. The two critical steps are: 1) confirming that the biomarker is associated with a treatment outcome ("clinical validity") and 2) demonstrating that biomarker collection improves a treatment outcome ("clinical utility"). Currently, there are a large number of biomarkers being tested that may someday prove to benefit patients, including measurement of drug concentrations and various physiological "pharmacodynamics" indicators, such as systemic estradiol concentrations in breast cancer patients receiving aromatase inhibitors. However, it is incumbent upon translational researchers to document the biomarker's clinical validity and utility prior to adoption into clinical practice.

Koolen and colleagues refer to a "minimum value for efficacy of approximately 6 ng/mL" for circulating endoxifen concentrations and cite a single retrospective study reporting this threshold. Our commentary noted two prospective clinical trials investigating the putative association between endoxifen concentration and tamoxifen treatment efficacy, neither of which confirmed clinical validity in preliminary results reported at ASCO 2016(2,3).

In this era of unsustainably increasing healthcare costs, particularly in cancer treatment, it is critical to practice evidence-based medicine. Given the lack of evidence of clinical validity

Correspondence: Daniel L Hertz, 428 Church St., Room 3054 College of Pharmacy, Ann Arbor, MI 48109-1065, Office phone: (734) 763-0015, Fax: (734) 763-4480, DLHertz@med.umich.edu.

Disclosures: No potential conflicts of interest

or utility, measuring endoxifen concentrations is practicing one of the alternatives to evidence-based medicine(4). If endoxifen concentration has been measured and found to be low, increasing the tamoxifen dose would be reasonable based on the documented safety of this approach(5), and could potentially enhance efficacy. However, an endoxifen threshold for efficacy has not been established and, at least until one is, clinicians should not measure endoxifen concentration to inform personalized tamoxifen treatment decisions.

References:

1. Hertz DL, Rae JM. Individualized Tamoxifen Dose Escalation: Confirmation of Feasibility, Question of Utility. Clin Cancer Res 2016;22(13):3121–3 doi 10.1158/1078-0432.ccr-16-0370. [PubMed: 27012810]
2. Lintermans A, Van Asten K, Jongen L, Blomme C, Lambrechts D, Van Calster B, et al. Prospective study evaluating the effect of impaired tamoxifen metabolisation on efficacy in breast cancer patients receiving tamoxifen in the neo-adjuvant or metastatic setting. ASCO Meeting Abstracts 2016;34(15_suppl):523.
3. Stearns V, O'Neill AM, Schneider BP, Flockhart DA, Skaar TC, Liu MC, et al. A phase II prospective trial correlating progression-free survival (PFS) with CYP2D6 activity in patients with metastatic breast cancer treated with tamoxifen: ECOG-ACRIN E3108. ASCO Meeting Abstracts 2016;34(15_suppl):546.
4. Isaacs D, Fitzgerald D. Seven alternatives to evidence-based medicine. Oncologist 2001;6(4):390–1. [PubMed: 11524559]
5. Hertz DL, Deal A, Ibrahim JG, Walko CM, Weck KE, Anderson S, et al. Tamoxifen Dose Escalation in Patients With Diminished CYP2D6 Activity Normalizes Endoxifen Concentrations Without Increasing Toxicity. The oncologist 2016;21(7):795–803 doi 10.1634/theoncologist.2015-0480. [PubMed: 27226358]