Curr Oncol, Vol. 20, pp. e612-613; doi: http://dx.doi.org/10.3747/co.20.1598

LETTER TO THE EDITOR

Weakly hormone receptor–positive breast cancer and use of adjuvant hormonal therapy

The Editor
Current Oncology
June 5, 2013

Breast cancer is the most common cancer affecting women[1], and estrogen receptor (ER)–positive breast cancer is the most common subtype[2]. An expert consensus meeting in 2009 on the primary therapy of early breast cancer asserted that adjuvant endocrine therapy, including tamoxifen and aromatase inhibitors, should be given according to breast cancer subtype as determined by hormone receptor (HR) testing[3]. The most common technique used for HR testing in the 1970s was ligand-binding assays, but they were replaced by immunohistochemistry (IHC) in the early to mid-1990s after that technique was shown to be equivalent or superior to the ligand-binding assay[4]. Immunohistochemistry has since been used to determine which patients should be offered adjuvant endocrine therapy[4], although the exact threshold for ER or progesterone receptor (PR) positivity has been debated. Data on the degree of benefit associated with adjuvant hormone therapy for weakly positive patients are insufficient[5], which has made the benefit–risk analysis challenging for physicians to perform for adjuvant hormonal therapy this patient population.

Before the 1999 publication of Harvey *et al.*[4], the use of adjuvant endocrine therapy in ER-positive patients was left to individual physician discretion. Historically, guidelines established a 10% threshold for ER or PR positivity, but evidence from several studies indicated that a response to tamoxifen therapy may be seen with as little as 1% of the tumour staining positive[2,4]. It is therefore currently recommended that adjuvant endocrine therapy be considered for breast cancer patients with any positive level of ER expression above the 1% threshold[2,3]. The same threshold applies to PR positivity. However, in the 1%–10% category, American Society for Clinical Oncology recommendations have added the proviso that "it is reasonable for oncologists to discuss the pros and cons of endocrine therapy with patients whose tumors contain low levels of ER (1%–10% weakly positive cells) by IHC, and to make an informed decision based on the balance"[2]. Data concerning the positive predictive value of low-level ER or PR expression—in the range of 1%–10% positive cells by IHC—are limited[3]. Furthermore, it is not known whether most patients with low levels of ER expression are actually being prescribed adjuvant hormonal therapy. We therefore undertook to determine whether hormonal therapy is being prescribed to patients with low ER positivity by IHC (1%–10% of cells positively stained, regardless of intensity) compared with patients with ER positivity greater than 10% (greater than 10% of tumour cells positively stained).

We reviewed 2018 consecutive patients seen at one institution from 2006 to 2011. The 1387 patients with invasive cancers staged T1c–T4 (*a priori* noninvasive or small tumours in which hormonal therapy might not be recommended as beneficial were excluded) had completed treatment. Of those patients, 46 were weakly ER- or PR-positive, and 29 of them received hormonal therapy. Another 1073 were strongly ER- or PR-positive, and 890 of them received hormonal therapy. The remaining 268 were ER-negative. Of all the ER-positive patients eligible for hormonal therapy, the percentage not prescribed adjuvant hormonal therapy was significantly higher in the weakly positive subgroup than in the strongly positive subgroup (17 / 46 = 37% vs. 183 / 1073 = 17%, $p = 0.0014$ by Fisher exact t-test).

In 88% of cases, weakly positive ER or PR patients who did not receive adjuvant endocrine therapy were described as being "ER/PR negative" in the dictations by their oncologists. In the remaining 12% of cases, the medical oncologist decided against the use of hormonal therapy based on low anticipated benefit.

Oncologists have struggled with managing weakly positive ER or PR patients, given a lack of data about the risks and benefits of adjuvant therapy in this low-expression range. After stratifying breast cancer patients into two categories of HR positivity, we discovered a significant difference in use of

adjuvant hormonal therapy between patients that were weakly and strongly positive.

Those results highlight a need to evaluate how decision-making for the use of adjuvant hormonal therapy might differ in weakly positive ER or PR patients. It appears that the decision not to give hormonal therapy to weakly positive ER or PR patients is a result of an interpretation of their receptor status as HR-negativity in 88% of cases, presumably based on earlier cut-off levels for what would be considered hormone-positive—highlighting the need for ongoing knowledge transfer as new tests, guidelines, and cut-off values are adopted in oncology.

Current practice patterns in the use of adjuvant hormonal therapy in weakly positive ER or PR breast cancer differ from those in strongly positive ER or PR breast cancer. Although patients with very low HR-positive expression levels derive an unclear magnitude of benefit from hormonal therapy, discussion of the use of adjuvant hormonal therapy in this patient population is encouraged.

Cassandra M. Lin BMSc
Schulich School of Medicine and Dentistry
University of Western Ontario
London, Ontario

Jasbir Jaswal MD
Schulich School of Medicine and Dentistry
University of Western Ontario
London, Ontario

Theodore Vandenberg MD
Schulich School of Medicine and Dentistry
University of Western Ontario
Department of Oncology
London Regional Cancer Program
London, Ontario

Alan Tuck MD
Schulich School of Medicine and Dentistry
University of Western Ontario
Department of Pathology
University of Western Ontario
London, Ontario

Muriel Brackstone MD
Schulich School of Medicine and Dentistry
University of Western Ontario
Department of Oncology
London Regional Cancer Program
Department of Pathology
University of Western Ontario
London, Ontario
muriel.brackstone@lhsc.on.ca

CONFLICT OF INTEREST DISCLOSURES

The authors have no financial conflicts of interest.

REFERENCES

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin* 2011;61:69–90.
2. Hammond ME, Hayes DF, Dowsett M, *et al.* American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. *J Clin Oncol* 2010;28:2784–95. [Erratum in: *J Clin Oncol* 2010;28:3543]
3. Goldhirsch A, Ingle JN, Gelber RD, Coates AS, Thürlimann B, Senn HJ. Thresholds for therapies: highlights of the St Gallen International Expert Consensus on the primary therapy of early breast cancer 2009. *Ann Oncol* 2009;20:1319–29.
4. Harvey JM, Clark GM, Osborne CK, Allred DC. Estrogen receptor status by immunohistochemistry is superior to the ligand-binding assay for predicting response to adjuvant endocrine therapy in breast cancer. *J Clin Oncol* 1999;17:1474–81.
5. Morgan DA, Refalo NA, Cheung KL. Strength of ER-positivity in relation to survival in ER-positive breast cancer treated by adjuvant tamoxifen as sole systemic therapy. *Breast* 2011;20:215–19.