Adjuvant Hormonal Therapy for Premenopausal Breast Cancer: Incorporating Clinical Experience

April 15, 2010
By Saira Nasim, MBBS, MRCPI [1] and Kathleen I. Pritchard, MD, FRCP [2]

The article “Adjuvant Hormonal Therapy in Premenopausal Women With Operable Breast Cancer: Not-So-Peripheral Perspectives” by Richard Love, published in this issue of ONCOLOGY, raises a number of important practice issues in the setting of adjuvant hormonal therapy for premenopausal women. This paper was written partially in response to Dr. Pritchard’s publication, “Ovarian Suppression/Ablation in Premenopausal ER-Positive Breast Cancer Patients,” which appeared in the January 2009 issue of this journal.[1] We would like first to comment on the general differences between that article and Dr. Love’s current paper.

The January 2009 paper was designed as an evidence-based review of the literature. In practice, however, we all must make decisions based on less robust data or in the absence of data. Furthermore, many of the issues raised by Dr. Love involve considerable, if not level 1, clinical and scientific evidence. In the current Program in Evidence-Based Care (PEBC) of Cancer Care Ontario (CCO), an explicit section is devoted to conclusions that extrapolate from evidence-based data to incorporate clinician concerns or experience from clinical practice.[2] Much of the information highlighted by Dr. Love fits into this category. These sections have been added to the CCO PEBC Guidelines because it is believed that there are often important approaches that may come only from the consensus of experts or from practical clinical experience. Several of the points Dr. Love raises belong in this category. In the following commentary, we respond to his seven issues.

Descriptive Epidemiologic Data of Breast Cancer Globally

We agree with Dr Love’s observation on changing global patterns in the incidence of breast cancer. It is no longer a disease confined to the Western world. Over a million new cases of breast cancer will be diagnosed worldwide each year. Low- and middle-income countries will be burdened by nearly half of these new breast cancer cases, which occur predominantly in premenopausal women, in contrast to the predominance of postmenopausal cases in affluent countries. Lack of data on reproductive risk factors, genetics, and metabolic profile in the majority of these women adds to the complexity of the global breast cancer burden worldwide. Screening and treatment approaches may also be quite different from those for Caucasian women living in Western countries. Treatment modalities such as tamoxifen or surgical oophorectomy, which are both efficacious and cost-effective, are important and acceptable therapeutic options for women in the low- and middle-income countries.

Tumor Hormonal Receptor Testing

Issues around quality control in this area have recently been widely publicized.[3,4] The upcoming American Society of Clinical Oncology (ASCO)–College of American Pathologists (CAP) estrogen receptor (ER)/progesterone receptor (PR) guideline addresses many of these issues, including tissue fixation, choice of antibody, method for interpretation of immunostaining, and other issues to ensure validation and standardization for ER testing.[5] Love’s discussion of the fact that 10% more tumors are found to be hormone receptor–positive in core biopsies than in lumpectomy and mastectomy specimens, is probably an illustration of the time to penetration and fixation of tumor tissues, which, as he describes, is probably longer in larger specimens. Clearly, if receptor analysis were done on cores only or on cores and lumpectomy/mastectomy specimens, more information could be obtained. This suggestion should indeed be further considered, and additional data regarding this
matter would be useful.

**Hormone Receptor-Positive Breast Cancer Is a Chronic Disease**

As we have collected and considered additional data concerning interim follow-up and treatment of hormone-positive breast cancer patients over the past 5 to 15 years, a paradigm shift has occurred. As Love points out, data such as those from the Early Breast Cancer Trialists’ Collaborative Group[6] and Saphner et al[7] clearly support this view. Unfortunately, lack of funding for long-term follow-up in many clinical cooperative groups has resulted in the discontinuation of follow-up after 10 years in many adjuvant trials. This is unfortunate in what is clearly a chronic disease for which long-term follow-up is becoming more, not less, important. Funding for long-term classic trial follow-up or new and cheaper approaches to long-term follow-up should clearly be explored. Excellent work in this regard has been done in some of the Scandinavian countries, where data from large randomized trials were matched with registry data to produce interesting outcome and toxicity results.[8]

**Combined Ovarian Suppression or Ablation and Tamoxifen Therapy Is Standard of Care**

Here we must take exception with Dr. Love. We agree that Dr. Gnant’s Austrian Breast Cancer Study Group (ABCSG) trial,[9] at least suggests that there is no benefit to the use of an aromatase inhibitor (AI) plus ovarian suppression in comparison to tamoxifen plus ovarian suppression. However, we think these are insufficient data to establish equivalence and that further follow-up of this study and/or additional data would be helpful.

Many have hypothesized that a luteinizing hormone-releasing hormone (LHRH) agonist plus an AI would be superior, assuming that ovarian suppression with an LHRH analog is always complete. This is clearly not so.[10,11] It is well known that 5% to 10% of normal premenopausal women receiving an LHRH agonist may override the agonist, particularly when 3-monthly LHRH analogs are given.[12] AIs, by lowering peripheral estrogen provide negative feedback to the pituitary, and in the premenopausal setting this feedback loop may result in overproduction of estrogen by the intact ovaries. Thus, an LHRH agonist plus an AI is, theoretically at least, unsafe, and in any case has not been adequately shown to be equivalent to tamoxifen plus an LHRH agonist. It is important to recognize, therefore, that clinicians should not use an LHRH agonist plus an AI in premenopausal women outside of clinical trials.

We also somewhat disagree with Love’s interpretation of the mini–meta-analysis[13] of the combination of LHRH plus tamoxifen compared to an LHRH agonist alone. This is a small meta-analysis driven almost completely by one study.[14] While it appears to suggest that an LHRH agonist plus tamoxifen is better in the metastatic setting than an LHRH agonist alone, the comparison to an LHRH agonist followed by tamoxifen vs the two used concurrently has not been well made. As a result, few clinicians have incorporated this concurrent combination into the metastatic setting. We believe that posing this question in the adjuvant setting will make both efficacy and toxicity much more clear. The Suppression of Ovarian Function Trial (SOFT) data will add to the evidence available regarding this question, but even SOFT may be somewhat underpowered. Since SOFT has now completed accrual, one can—and we certainly do—discuss the use of tamoxifen alone, ovarian suppression or ablation alone, or the combination as therapeutic options in all premenopausal women with hormonally responsive breast cancer in the adjuvant setting.

**Pharmacogenetic Hypotheses With Tamoxifen**

Dr. Love has succinctly summarized the issues of tamoxifen pharmacogenomics. Side effects associated with tamoxifen and variation in response have been identified since initial drug development. The clinical relevance of CYP2D6 genotyping remains uncertain, as currently available evidence is contradictory. None of the published studies have assessed the association of endoxifen, the most important tamoxifen metabolite, with clinical outcomes in breast cancer patients. We agree that this remains a matter for further study and requires evaluation in terms of the clinical utility of monitoring endoxifen levels when steady-state metabolite concentrations are reached after 4 weeks.
of continuous tamoxifen therapy.[15] It may be more useful to determine CYP2D6 genotype prior to commencing tamoxifen rather than to attempt therapeutic drug monitoring. Additional data from well designed clinical trials will clearly be useful in this setting before a change in practice is advocated.

**Ethical Issues in Ovarian Suppression vs Ablative Treatment**

In a single payer and perhaps more fiscally accountable system such as the Canadian or Ontario Health Care System, preference toward surgical oophorectomy, rather than ongoing LHRH agonists, is clear. However, it is our practice that LHRH agonists may be used to test a patient’s tolerance to ovarian ablation before performing surgery and/or in settings in which preservation of subsequent ovarian function is desired in order to facilitate pregnancy or for other reasons. Nonetheless, surgical oophorectomy is definitely preferable—both clinically and financially—once permanent oophorectomy is decided on between patient and physician. In many patients who are over 40 or 45 years old and/or who do not desire future pregnancies, this is an easy decision. We do believe however, that the use of LHRH agonists should remain an option for women who desire only temporary ablation for a variety of personal reasons. Nonetheless, as Dr. Love points out, this approach raises the issue of length of administration of LHRH agonists, which has not been well studied.

**Importance of Primary Tumor Removal and Surgical Stress in Solid Tumor Management**

The impact of the timing of breast surgery according to the phase of menstrual cycle has been a controversial issue, and current available evidence is contradictory.[16-19] Problems in evaluating this hypothesis are exacerbated by the difficulty of accurate assessment of the hormonal status of the patient as well as the challenge of scheduling a patient’s surgery to fit with her hormonal cycle, particularly with tight operating schedules, and the frequent disruption of hormonal cycling after breast cancer diagnosis. While this hypothesis has strong preclinical support and may be correct, we suspect it will remain poorly tested and not practical for regular usage.

**Conclusion**

Dr. Love raises a number of important issues. These include viewing breast cancer as a worldwide, rather than a Western disease, as well as the role of clinician consensus and experience in informing physical practice. Clearly, further investigation of concurrent combination vs sequential hormonal approaches in adjuvant therapy and of the pharmacogenetics of tamoxifen will provide additional evidence in these important areas.

**References**


5. Osborne CK: CAP and ASCO join to develop ER/PR guidelines (special scientific presentation).


**Source URL:**

**Links:**
[1] [http://www.diagnosticimaging.com/authors/saira-nasim-mbbs-mrcpi](http://www.diagnosticimaging.com/authors/saira-nasim-mbbs-mrcpi)
[2] [http://www.diagnosticimaging.com/authors/kathleen-i-pritchard-md-frcp](http://www.diagnosticimaging.com/authors/kathleen-i-pritchard-md-frcp)