Adjuvant Hormonal Therapy in Premenopausal Women With Operable Breast Cancer: Not-So-Peripheral Perspectives

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By Richard R. Love, MD, MS [2]

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While optimal adjuvant hormonal therapies for premenopausal women with operable breast cancer have yet to be defined, discussions and reviews of the state of the art and “areas of confusion” often fail to consider developments that are germane to keeping evidence-based clinical practice truly up-to-date. The current communication is prompted by this perspective and a recent review and its commentaries.[2]

The late Jonathan Mann often said that the way we frame issues dictates how we approach them. Framing the challenges of getting to more effective adjuvant therapies for premenopausal women with hormone receptor–positive tumors within the context of our most recent and ongoing larger clinical trials only—which is what is usually done—is to ignore the richness and relevance of other provocative and emerging data that are directly applicable to clinical and investigative practice now. Here, I review such data in seven areas.

Descriptive Epidemiologic Data of Breast Cancer Globally

There are several reasons why we need to move away from perspectives and data based on North America only (or high-income countries only) in discussing breast cancer management. First, the cancer treatment and reading community is global, and we are increasingly called upon to be global citizens and speak to the needs of patients everywhere. In 2010, we will move to situations in which, worldwide, the majority of new annual cases of breast cancer will develop in Asian women (~800,000 of 1.5 million) and half will be in poor premenopausal women (~740,000 vs 44,000 premenopausal cases in the United States).[3,4]

Further, the fact that the overwhelming majority of our treatment data come from studies in women of northern European genetic background—with likely very specific tumor gene profiles and certainly different metabolic gene profiles—make the available data of uncertain relevance to this new majority of affected women who live in non-Western countries, as well as those women in Western countries of different genetic/ethnic backgrounds.[5-7] Finally, a common perception is that hormone receptor–positive breast cancer is less frequent in pre- than in postmenopausal women, but data from the Philippines, Vietnam, Taiwan, and China do not support this general conclusion.[8,9, and personal communications from Zhi Ming Shao, November 7, 2009; and from Ta Van To, May 2009] In sum, our discussions about breast cancer management need to be more broadly sensitive and considerate of the global realities.

Tumor Hormonal Receptor Testing

While for some time there have been expressions of concern regarding quality control issues surrounding tumor hormonal receptor testing, the implications for practicing clinicians (and possible remedial actions) have not been obvious. With the upcoming publication of the American Society of Clinical Oncology (ASCO)–College of American Pathologists (CAP) guidelines on hormonal receptor quality assurance, this situation should change. In the meantime, various data regarding one broad issue, which will be addressed in the guidelines, deserve all clinicians’ attention: choices of tissue specimens and their management prior to laboratory testing.

The relevant data include time to penetration and fixation of subsequently tested tumor tissues (optimally < 30 minutes), pH of fixative (optimally neutral, not acidic), and duration of fixation (optimally > 8–10 hours; less critically < 48 hours). Each of these factors influence determination of
the presence and levels of hormonal receptor proteins.[10-12] Inattention to these parameters leads
to more frequent findings of hormone receptor–negative tumors and lower levels of hormonal
receptor proteins. When hormonal receptor determinations are done on core biopsy specimens,
approximately 10% more tumors are found to be hormone receptor–positive, compared with when
tests are done on subsequent mastectomy (and lumpectomy?) specimens.[13,14] The implications of
these findings are clear:
• False-negative findings of hormonal receptor protein lead to depriving patients of important,
recurrence-preventing hormonal therapies and in many circumstances choices of usually more toxic
chemotherapy treatments.
• Clinicians need to be involved in the complete management sequence of tissue specimens
obtained when hormonal receptor testing is part of the diagnostic panel.
• The diagnostic sequence for breast masses may, in some circumstances, need reconsideration.
When the sequence includes a fine-needle aspiration biopsy, and hormonal receptor determinations
are then done on subsequent mastectomy (as practiced in most of the world) or lumpectomy
specimens, even greater attention to tissue management procedures is warranted. The case for core
biopsy as the first diagnostic procedure, with this specimen used for hormonal receptor testing and
with associated attention to optimal tissue management, deserves renewed consideration.

Hormone Receptor–Positive Breast Cancer as a Chronic Disease

Data from multiple sources are reinforcing what clinicians have been aware of for some time, but
this awareness has not yet completely translated into thoughtful clinical practice and investigative
medicine. For example:
• Measurable and steady rates of recurrence characterize meta-analysis populations of patients with
hormone receptor–positive breast cancer (more so than those with hormone receptor–negative
tumors) through 15 years after diagnosis.[15,16] There is a lag in return to higher rates of
recurrence in the immediate years after hormonal therapies are stopped (eg, ~5 years).[15,17-19]
• In cases where hormonal therapies are given for longer than 5 years or started after 5 years from
diagnosis, lower rates of recurrence occur in the 5- to 10-year postdiagnosis window.[17,20-22]

Current National Comprehensive Cancer Network (NCCN) guidelines suggest the use of adjuvant
hormonal therapy with an aromatase inhibitor after 5 years (ie, for postmenopausal women, a status
that all premenopausal women can achieve with chemotherapies, ovarian ablation, or continuing
suppression therapies). However, there does not appear to be a consensus on this recommendation,
at least as manifested in recommendations for therapies after 5 years in ongoing adjuvant studies.
Clearly, there are many uncertainties about risks and benefits for subsets of patients, but the clear
conclusion that hormone receptor–positive breast cancer is, for many (and perhaps the majority of
patients), a chronic disease, must command more of our collective attention. Part of the reticence to
more frequently and forthrightly consider this issue comes from the fact that patients find this to be
an upsetting perspective, particularly because this is not how the disease has been framed in the
past.

Combined Ovarian Suppression/Ablation and Tamoxifen Therapy as the
Standard of Care

In 2003–2004, it may have been reasonable to assert that tamoxifen alone was the hormonal
therapy standard of care for premenopausal women with hormone receptor–positive tumors. This
was the conclusion of the Suppression of Ovarian Function Trial (SOFT) investigators, who assessed
tamoxifen vs ovarian function suppression or ablation plus tamoxifen vs ovarian function
suppression or ablation plus an aromatase inhibitor ( exemestane [Aromasin]), giving each therapy
for 5 years.[2] Many in the research community have continued to maintain that tamoxifen alone is
the standard of care in this setting.

Austrian investigators reporting on the issue of ovarian suppression plus tamoxifen or an aromatase
inhibitor (trial discussed below), whose study began accrual in 1999, apparently did not consider
tamoxifen alone to be the standard of care a decade ago.[23] In 2009–2010, however, it is neither
reasonable nor appropriate to assert (1) such equivalence of tamoxifen alone and combined therapy,
and (2) to call for continued accrual to SOFT and the Tamoxifen/Exemestane Trial (TEXT),
withholding judgment on the role of aromatase inhibitors in combined therapy until these trials
report their results. The following findings support these contentions:
• In metastatic hormone receptor–positive disease, four individual trials and a meta-analysis have
demonstrated improved outcomes with combined ovarian suppression plus tamoxifen therapy over either therapy alone.[24,25]  
- In a large Intergroup trial, luteinizing hormone-releasing hormone (LHRH) alone after CAF chemotherapy (cyclophosphamide, doxorubicin [Adriamycin], fluorouracil [5-FU]), was inferior to LHRH plus tamoxifen (disease-free survival difference at 9 years = 8%; overall survival difference at 9 years = 3%).[26] In the metastatic setting, LHRH alone and tamoxifen alone appear to be equivalent therapies.[27]  
- Meta-analysis of adjuvant data suggests that the combination of LHRH plus tamoxifen is better than tamoxifen alone.[28]  
- In the Intergroup adjuvant trial, oophorectomy plus tamoxifen produced a disease-free survival rate of 90.3%, compared to 87.8% for tamoxifen alone.[29]  
- In two European adjuvant trials, LHRH plus tamoxifen was superior to six cycles of IV CMF chemotherapy (cyclophosphamide, methotrexate, 5-FU), while LHRH alone was equivalent to six cycles of Bonadonna CMF chemotherapy.[30,31]  
- In the author’s adjuvant trial of oophorectomy plus tamoxifen, this strategy resulted in a risk reduction of 0.58; in the meta-analysis of trials assessing adjuvant tamoxifen alone in premenopausal women, the risk reduction was 0.42.[15,19]  
The consistency of the evidence—although mostly indirect—and the logic that two mechanisms of action are functioning with combined therapy, make the superiority of combined ovarian suppression plus tamoxifen therapy difficult to ignore. The repeated counterargument is that direct evidence is needed, and the SOFT and TEXT trials will provide this. For the two hypotheses under investigation in those trials, this argument deserves careful scrutiny. However, compelling direct evidence is already available. Gnant et al presented survival data from the Austrian Breast and Colorectal Cancer Study Group (ABCSG)-12 trial comparing LHRH plus anastrozole (Arimidex) and LHRH plus tamoxifen with or without zoledronic acid (Zometa) in premenopausal women with hormone receptor-positive breast cancer.[23] A 2×2 factorial design was used (1:1:1:1), with patients randomized to LHRH plus either anastrozole or tamoxifen, with or without zoledronic acid. The study enrolled 1,803 patients and was designed to test two primary hypotheses for the outcome of disease-free survival: (1) anastrozole against tamoxifen, and (2) zoledronic acid against no zoledronic acid.  
While the addition of zoledronic acid exhibited a significant benefit in terms of disease-free survival, no difference in disease-free survival was found between the anastrozole and tamoxifen groups (P=.59, hazard ratio [HR] = 1.10, 95% confidence interval [CI] = 0.78–1.53). A similar pattern was seen for recurrence-free survival (P=.53, HR = 1.11, 95% CI = 0.80–1.56), and a trend for overall survival was found in favor of tamoxifen (P=.07, HR=1.80, 95% CI: 0.95–3.38).[23] While a failure to reject the null hypothesis in a trial designed to test for superiority does not allow us to conclude the treatments are equivalent, there is no evidence from these data to support the superiority of anastrozole over tamoxifen in this population. However, given the size of this trial, the maturity of the data (median follow up of 48 months), and the pattern and trend of results, there is little justification for the position that the superiority of anastrozole compared with tamoxifen after ovarian ablation or with ovarian suppression alone remains an open question. Thousands of further patients and years of follow-up will be required to demonstrate even a small effect, and these Gnant results would have to be considered in reaching conclusions about the “true” comparison results. Both the SOFT and TEXT trials also allow chemotherapy treatment. Looking to these trials for a different answer to the question of aromatase inhibitor or tamoxifen superiority in premenopausal women whose ovarian function is stopped, is neither appropriate nor realistic. While a definitive conclusion cannot be drawn from the Gnant study in terms of the survival benefits of anastrozole over tamoxifen in the premenopausal setting, a reasonable decision is to proceed as though the treatment results are similar.  

Pharmacogenetic Hypotheses About Tamoxifen  
The role of metabolic activation in tamoxifen activity was recognized in the 1970s, when the minor metabolite of tamoxifen, 4-hydroxytamoxifen, was shown to have 100-fold greater affinity than tamoxifen toward estrogen receptors and subsequently 30- to 100-fold greater potency than tamoxifen in suppressing estrogen-dependent cell proliferation.[32] However, the contribution of this metabolite to the overall clinical effect of tamoxifen has remained unclear because its plasma concentrations are relatively low compared with those of tamoxifen or some of its other metabolites. Our knowledge of the link between tamoxifen metabolism and response expanded rapidly
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The limited surgical oophorectomy data have allowed this LHRH approach to be promulgated as the standard of care worldwide, a standard that is not practical for the majority of women who need ovarian ablation. At $18,000 and $30,000 for 3 and 5 years of therapy, respectively, the economic cost is significant. At $500 or more per month, a year of LHRH treatment is $6,000 in direct costs, not counting the inconvenience and need to continue LHRH therapy indefinitely. On the cost side for LHRH agonists, inconvenience and the need to assess for biologic effect are practical considerations, tied together with the major issue of reversibility. On the benefit side for LHRH treatment, reversibility is touted as important. This benefit is less certain given the “same” outcomes—ovarian function suppression and chronic tumor growth factor reduction.[57] On comparison in high-income countries has been to use LHRH agonists and surgical oophorectomy are associated with similar outcomes.[55,56] The data on this adjuvant comparison in ovarian ablation (by surgery or radiation therapy) as practiced in the 1970s was, contrary to previous beliefs, likely to be effective, the practice in high-income countries has been to use LHRH agonists to achieve the “same” outcomes—ovarian function suppression and chronic tumor growth factor reduction.[57] On the benefit side for LHRH treatment, reversibility is touted as important. This benefit is less certain when the question of optimal duration of therapy is considered. In prostate cancer, clinicians often continue LHRH therapy indefinitely. On the cost side for LHRH agonists, inconvenience and the need to assess for biologic effect are practical considerations, tied together with the major issue of economic cost. At $500 or more per month, a year of LHRH treatment is $6,000 in direct costs, leading to costs of $18,000 and $30,000 for 3 and 5 years of therapy, respectively. The limited surgical oophorectomy data have allowed this LHRH approach to be promulgated as the standard of care worldwide, a standard that is not practical for the majority of women who need surgical oophorectomy.

Ethical Issues in Ovarian Suppression vs Ablative Treatment

In metastatic hormone receptor–positive breast cancer, treatments with LHRH agonists and surgical oophorectomy are associated with similar outcomes.[55,56] The data on this adjuvant comparison in premenopausal women are too limited and indirect to reach a conclusion, but there is no reason to expect incomparability, except on the question of the duration of LHRH therapy.[15,28] From the time of the first meta-analysis report suggesting that adjuvant ovarian ablation (by surgery or radiation therapy) as practiced in the 1970s was, contrary to previous beliefs, likely to be effective, the practice in high-income countries has been to use LHRH agonists to achieve the “same” outcomes—ovarian function suppression and chronic tumor growth factor reduction.[57] On the benefit side for LHRH treatment, reversibility is touted as important. This benefit is less certain when the question of optimal duration of therapy is considered. In prostate cancer, clinicians often continue LHRH therapy indefinitely. On the cost side for LHRH agonists, inconvenience and the need to assess for biologic effect are practical considerations, tied together with the major issue of economic cost. At $500 or more per month, a year of LHRH treatment is $6,000 in direct costs, leading to costs of $18,000 and $30,000 for 3 and 5 years of therapy, respectively. The limited surgical oophorectomy data have allowed this LHRH approach to be promulgated as the standard of care worldwide, a standard that is not practical for the majority of women who need surgical oophorectomy.
treatment. In the face of the available data, it is inappropriate and ethically untenable to continue this stance. Surgical oophorectomy should be the global standard of care for premenopausal women with hormone receptor-positive tumors.

**Primary Tumor Removal and ‘Surgical Stress’ in Solid Tumor Management**

For many years it has been known that removal of primary tumors is associated with facilitation of the growth of micrometastatic disease. Hrushesky and colleagues have highlighted the often observed increase and peak in hazard for the appearance of clinical metastatic disease in the immediate 2 to 3 years following removal of primary breast cancers. These investigators hypothesized that perioperative factors can be manipulated to decrease this hazard.[58] Despite confirming data in various studies that this hazard peak is not a statistical artifact and must be anchored by the event of primary tumor removal, primary breast surgery has continued to be seen as a technical intervention.

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Exploratory early and longer-term data have suggested that concurrent (same day) surgical oophorectomy and primary breast surgery is characterized by significant benefit from oophorectomies done in the luteal phase of the menstrual cycle.[59,60] We have offered a “progesterone trigger hypothesis” to explain this observation: Rapid decreases in progesterone blood levels in the luteal phase of the menstrual cycle with oophorectomy lead to “downstream” angiogenic protein changes that block micrometastatic growth.[61] A recent elegant laboratory research report has offered complementary evidence that perioperative, proangiogenic surgical stress–induced changes can be manipulated with reductions in tumor growth.[62] These observations all strongly suggest that greater attention to perioperative tumor biology growth models is warranted. We have two phase III proof-of-principle clinical trials in breast cancer testing our oophorectomy timing hypothesis.

**Conclusions**

The descriptive epidemiology of breast cancer—in terms of global case burdens, now predominantly
an Asian and premenopausal disease—and the realization that the majority of the available biologic and treatment data come from high-income populations with northern European genetic backgrounds, should temper our discussions of breast cancer treatment. Tumor specimen selection and management before hormonal receptor testing are critical in influencing the likelihood of finding the presence of estrogen and progesterone receptor proteins. Both clinicians and patients should view hormone receptor-positive breast cancer as a commonly chronic disease.

In premenopausal women, combined hormonal therapy with ovarian ablation or suppression and tamoxifen therapy is the standard of care, and the ongoing SOFT and TEXT studies are very unlikely to provide support otherwise. The pharmacogenetic data with respect to tamoxifen are currently insufficient to dictate clinical practice. Specific prospective trials investigating the hypothesis that endoxifen concentrations in individual patients predict therapeutic efficacy are urgently needed. The high economic cost of LHRH treatment compared to that of surgical oophorectomy, given repeatedly demonstrated comparability of therapeutic effects, suggest that surgical treatment should be the standard of care. Finally, perioperative primary tumor biology warrants significantly more attention as we seek better approaches to breast cancer control that are practical and inexpensive, and produce limited side effects.

References:


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