Hormonal therapy for breast cancer patients is one of the oldest targeted treatments in cancer care. Many issues about their optimal use remain to be resolved, however. For postmenopausal women, questions include the relative benefits and drawbacks of using tamoxifen vs the aromatase inhibitors vs both sequentially, and optimal duration of therapy. Research into the effect of individual women’s genetically determined metabolism on the efficacy and side effects of hormonal therapies may contribute important information to establish optimal treatment for this group. For breast cancers in premenopausal women, the use of hormonal therapy in combination with ovarian ablation is under investigation, including the potential role of aromatase inhibitors.

Hormonal therapy for treatment of breast cancer was one of the first “targeted” treatments developed for cancer: testing of estrogen and progesterone receptor status of tumours, to determine if hormonal therapy would be beneficial, has become standard practice.

**CURRENT STRATEGIES AND ISSUES FOR POSTMENOPAUSAL WOMEN**

As approximately 60% to 70% of postmenopausal women have hormone receptor-positive disease, the majority of postmenopausal women receive hormonal therapy — tamoxifen or aromatase inhibitors — and for those with low risk of recurrence it may be the only systemic treatment after surgery.

Tamoxifen is a selective estrogen receptor modulator (SERM). It acts as an antiestrogen at the level of the breast cancer cell but has estrogenic activity at other target organs such as bone and endometrium. Because the source of estrogen does not affect the efficacy of tamoxifen, it is of value for women both before and after menopause. In postmenopausal women, however, the main source of estrogen is derived from the conversion of androstenedione and testosterone via the aromatase enzyme, which is found in skeletal muscle, fat and other tissues. Aromatase inhibitors (anastrozole, letrozole) and inactivators (exemestane) effectively suppress the production of estrogen through this pathway, making levels of circulating estrogen extremely low and “starving” estrogen-dependent breast cancer cells of stimulation by this hormone.

The 2000 Early Breast Cancer Trialists’ Collaborative Group overview reaffirmed the value of tamoxifen in women with estrogen receptor-positive (ER-positive) breast cancer. To date, 2 trials, the Arimidex, Tamoxifen, Alone or in Combination (ATAC) (tamoxifen vs anastrozole) and BIG 1-98 (tamoxifen vs letrozole) trials, are showing an improvement in disease-free survival for the aromatase
inhibitors (AIs) over tamoxifen but no statistically significant overall survival advantage — at least not yet. A similar benefit in disease-free survival advantage is seen when using a switch strategy: tamoxifen for 2–3 years followed by either exemestane (IES trial) or anastrozole (Jonat et al’s 2006 meta-analysis). The BIG 1-98 study is evaluating the potential benefit of treating with an AI and then switching to tamoxifen. The advantage of a switch strategy may be due to decreased time of exposure to each agent (SERM and AI) — which may result in decreased incidence of toxicities. Use of tamoxifen is associated with the development of uterine cancer and a greater risk of thromboembolism, and AIs are associated with osteopenia and osteoporosis, with resulting fracture risk. Both agents are associated with menopausal symptoms such as hot flashes and vaginal discharge and/or dryness.

When given as monotherapy, the current recommendation of duration for tamoxifen is 5 years. Two trials are exploring longer duration of tamoxifen: the Adjuvant Tamoxifen Treatment — Offer More! (aTTom) trial and the Adjuvant Tamoxifen Longer Against Shorter (ATLAS) trial. Sir Richard Peto presented preliminary results of the ATLAS trial at the 2007 San Antonio Breast Cancer Symposium (SABCS). This international trial randomized 11,500 women (59% ER-positive and 41% ER-untested) to receive either 5 or 10 years of tamoxifen. In these preliminary results, around 1500 recurrences have been reported — about 1300 during years 5–9, but only about 200 during years 10–14. Breast cancer mortality and overall mortality were lower among those randomized to continue tamoxifen, but the differences were not statistically significant. Results from both aTTom and ATLAS are expected in 2010.

The National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG) MA17 trial is looking at the question of extended therapy with letrozole following 5 years of tamoxifen, and shows an improvement in disease-free survival. The issue of how long extended therapy should continue has not been determined — thus results of the re-randomization of this trial, MA17R, to a further 5 years of letrozole for a total of 10 years will be of great interest.

PHARMACOGENETICS AND METABOLISM OF HORMONAL THERAPIES
Pharmacogenetics is becoming increasingly relevant to issues surrounding use of hormonal therapies in adjuvant treatment of breast cancer, and pharmacogenetic characteristics of individual patients are expected to eventually contribute to treatment decisions. It appears that some individuals may not metabolize drugs such as tamoxifen to the active metabolite.

Tamoxifen
Tamoxifen is metabolized by CYP2D6, a member of the cytochrome P450 family, to the active metabolite endoxifen. Levels of endoxifen are known to vary with the number of mutant alleles of the CYP2D6 gene. Several variants resulting from single nucleotide polymorphisms are known to reduce CYP2D6 activity, thereby decreasing endoxifen levels — particularly in homozygous (CYP2D6 *4/*4) women, known as poor metabolizers. The DNA testing can be done on blood samples using allele-specific polymerase chain reaction (AS-PCR) or the Affymetrix CYP450 GeneChip assay. When CYP2D6 *4/*4 women receive tamoxifen, they have shorter relapse-free survival and also experience fewer hot flashes. Dr. Stacey Knox presented a study at the 2006 American Society of Clinical Oncology (ASCO) Annual Meeting on women treated with tamoxifen, confirming that CYP2D6 *4/*4 women have worse recurrence-free survival (hazard ratio [HR] = 2.2, p = 0.02) than those with 0–1 mutations, and that this group also experienced fewer hot flashes.

A study presented at the 2007 ASCO meeting supported Knox et al’s suggestion that the side effects (i.e. hot flashes) experienced by women on tamoxifen and the agent’s efficacy are linked, and are related to the pharmacogenetic genotype. Utilizing data from The Women’s Healthy Eating and Living (WHEL) trial, Mortimer et al examined whether women who experience more hot flashes while taking tamoxifen have better outcomes than those with fewer hot flashes, and thus whether hot flashes may be a useful indicator of tamoxifen efficacy and prognosis. The WHEL trial enrolled 3088 women with breast cancer (Stages I – IIIA) within 2–48 months of initial diagnosis, and randomized them to either receive a dietary intervention (n = 1537) or to a control group (n = 1551). Disappointingly, the dietary intervention failed to provide a decrease in recurrence rates after seven years of followup. However, Mortimer et al’s analysis showed that among the 864 women in the control arm who were treated with adjuvant tamoxifen and about whom sufficient information was gathered, 78% reported hot flashes, and 69% of these also reported night sweats. Another 4% reported night sweats but no hot flashes, and 18% reported neither vasomotor symptom. At median followup of 7.3 years, breast cancer events occurred in 12.9% of the women with hot flashes vs 21% of those without (p = 0.01). The HR for recurrence during the followup period for women reporting hot flashes was 0.50 (95% CI 0.36 to 0.69). In fact, occurrence of hot flashes was more predictive of outcome for tamoxifen-treated patients than were age, tumour grade, hormone receptor status or initial disease stage.

Punglia et al created a Markov model using annual recurrence risks from the BIG 1-98 trial. BIG 1-98 randomized postmenopausal women with early breast cancer who were candidates for hormonal therapy to 4 treatment strategies: tamoxifen for 5 years, letrozole for 5 years, tamoxifen for 2 years followed by letrozole for 3 years and letrozole for 2 years followed by tamoxifen for 3 years. Based on previous data, the assumption was made that 6.8% of the population would be homozygous (CYP2D6 *4/*4) and 21.1% would be heterozygous (*4/wild type [wt]), and that the HR for increased cancer recurrence for women taking tamoxifen is 1.86 among *4/*4 carriers relative to those with wt/wt or wt/*4 genotypes. Modelling suggested that patients without CYP2D6 mutations (wt/wt) may have superior outcomes if initially treated with tamoxifen. These results suggest that tamoxifen may be equal — and possibly superior — to treatment with an AI for patients without CYP2D6 mutations, and raise the question of whether testing for CYP2D6 polymorphisms...
could help develop optimal hormonal treatment strategies for different women.

Schroth et al.\textsuperscript{11} recently reported a study that looked at breast cancer treatment outcome with adjuvant tamoxifen relative to CYP2D6 and CYP2C19 genotypes. Two allele variants at CYP2D6 and 2 at CYP2C19 passed the multiple-comparison adjustment, and showed significant associations with clinical outcome in the patients treated with tamoxifen, but not in the control group (who received no tamoxifen). CYP2D6 null alleles *4 and *5 were associated with a higher frequency of relapse (odds ratio = 2.13, 95% CI 1.26 to 3.63, empirically adjusted p-value = 0.03). The unadjusted odds ratio showed a 2- to 3-fold increased risk of relapse for CYP2D6 genotype individuals with at least one null allele. Other studies have not shown a similar correlation,\textsuperscript{16-18} and prospective studies are needed.

It is important to recognize that certain medications taken concomitantly with tamoxifen, notably selective serotonin reuptake inhibitors (SSRIs), can inhibit CYP2D6 and may affect the metabolism of tamoxifen, with a negative impact on the benefit derived.\textsuperscript{19} Figure 1 shows effects of some commonly used SSRIs on endoxifen levels.

All these studies suggest that pharmacogenetic testing may play a future role in selecting the optimal hormonal strategy for individuals with hormone-responsive breast cancer — an encouraging prospect. It is particularly interesting to think that hot flashes may be a surrogate biomarker of response to tamoxifen. Larger numbers of women will need to be studied to examine this question.

**Related research**

For now, the main predictors of response to hormonal therapy in postmenopausal women remain estrogen and progesterone receptor status. To learn more about metabolism and biochemical effects of aromatase inhibitors, the Indiana University School of Medicine and the Mayo Clinic recently launched an observational study (NCT00283608) that will examine whether breast cancer patients treated with AIs who have different responses to them, including bone loss and/or decrease in breast density, share genetic similarities. Another study, available to eligible Canadian women in 6 provinces, is the Phase III Trial Assigning Individualized Options for Treatment (Rx) (TAILORx, NCIC-MAC12, NCT00310180) trial.\textsuperscript{20} TAILORx is examining whether the Oncotype DX assay, a tool for molecular signatures and multigene analysis, can determine which women with hormone receptor-positive, node-negative breast cancer will respond to hormonal therapy and may not require chemotherapy, as previously implied by previous research.\textsuperscript{21} Over 10,000 women with hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative tumours will be enrolled, and those with intermediate-risk scores on the Oncotype DX assay will be randomized to receive either hormone therapy alone or chemotherapy followed by hormonal therapy.

**HORMONAL THERAPY IN PREMENOPAUSAL BREAST CANCER**

The advent of aromatase inhibitors and inactivators as options for postmenopausal women with hormone receptor-positive breast cancer raises the question of whether these drugs may be of value in the setting of the younger premenopausal patient. Tamoxifen has been the gold standard of hormonal therapy, including for premenopausal women, following results of the Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) meta-analysis in 1998.\textsuperscript{22}

**The role of ovarian suppression**

The benefit of ovarian function suppression in women receiving chemotherapy has been difficult to evaluate because of the confounding effects from chemotherapy on the ovaries, both temporary and permanent. Several European studies have compared ovarian function suppression with or without tamoxifen to combination chemotherapy in premenopausal women.\textsuperscript{23,24} The results have been similar in terms of outcomes, showing a benefit of the gonadotropin-releasing hormone (GnRH) agonist goserelin, with or without tamoxifen, added to standard therapy (ZIPP trial),\textsuperscript{23} or equivalence of goserelin to cyclophosphamide + methotrexate + fluorouracil (CMF) chemotherapy alone among ER-positive cases (ZEBRA trial).\textsuperscript{22} These results are difficult to translate to North American practice because the chemotherapy regimens used have tended to be non-anthracycline- and non-taxane-based.

A meta-analysis presented by Dr. Paolo Carlini at the 2007 ASCO\textsuperscript{24} analyzed the effects of ovarian ablation (OA) using GnRH agonists in premenopausal women with breast cancer,
using data from 15 eligible randomized-controlled trials (12,545 patients). Comparisons were made between OA + tamoxifen vs chemotherapy alone, OA ± chemotherapy ± tamoxifen vs chemotherapy alone, OA ± tamoxifen vs tamoxifen alone, and OA alone vs chemotherapy alone. The addition of ovarian ablation to chemotherapy, both with and without tamoxifen, provided statistically significant longer disease-free survival, but evidence for longer overall survival was seen only in the comparison of OA ± chemotherapy ± tamoxifen vs chemotherapy-only.

AROMATASE INHIBITORS

The use of AIs in hormone receptor-positive premenopausal women who have developed chemotherapy-induced amenorrhea is not advised at this time, as a recent case series showed that about 25% of women may regain ovarian function despite use of AIs.26 However, Rossi et al have recently reported that letrozole in combination with the GnRH agonist triptorelin induces more intense estrogen suppression than tamoxifen + triptorelin in premenopausal women with early breast cancer27 — as previously demonstrated in the postmenopausal population.

Two prospective trials, the Suppression of Ovarian Function Trial (SOFT, NCIC- MAC4, NCT000666990), accrual ongoing, and the Tamoxifen and Exemestane Trial (TEXT, NCIC- MAC5, NCT00066807),28 accrual completed in 2007, are assessing the role of ovarian function in conjunction with AIs and are expected to reveal the additional benefits, if any, of ovarian suppression in the management of breast cancer in premenopausal women. SOFT remains open to enrollment of Canadian women in many treatment centres across 6 provinces. Women who are premenopausal, have ER/PR-positive tumours and who either remain premenopausal within 6 months post-chemotherapy or are receiving tamoxifen as their only adjuvant treatment are randomized to receive either tamoxifen for 5 years, ovarian suppression (via either triptorelin for 5 years, oophorectomy or ovarian radiation) + tamoxifen for 5 years, or ovarian suppression + exemestane for 5 years. The trial opened in October, 2003; target enrollment is 3000 patients in the U.S., Canada, Europe, South America and India. TEXT, also international, enrolled premenopausal women with ER/PR-positive tumours within 12 weeks after surgery, prior to receiving adjuvant chemotherapy, to receive either triptorelin + tamoxifen for 5 years (with or without chemotherapy, as per investigator choice) or triptorelin + exemestane for 5 years, again with or without chemotherapy. The tamoxifen therapy in TEXT began 6–8 weeks after the start of triptorelin or chemotherapy. TEXT also opened in 2003, and is now closed as the required 1845 patients were accrued.

Results of these 2 prospective trials are expected to address the role of ovarian suppression in premenopausal women and whether aromatase inhibitors in combination with ovarian suppression offers an additional benefit over tamoxifen with or without ovarian suppression.

Disclosure

Dr. Walley reports no potential conflicts of interest relevant to this article.

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