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Review

Hormonal therapy in breast cancer: A model disease for the personalization of cancer care

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ABSTRACT

The treatment of breast cancer is driven by subtype classification, of which the assessment of hormone receptor status is one of the important determinants of therapy. The use of hormonal therapy to treat estrogen-receptor positive breast cancer has been studied for over a century and is one of the well-described uses of personalized medicine. In this review, we will describe the classification of hormone receptor status and the various endocrine treatment strategies. Opportunities for personalization of care are illustrated.

1. Introduction

The molecular diversity observed in breast cancer clearly illustrates the need for personalized medicine in the treatment of this disease. Breast cancer is one of the prototype cancers for which there is an abundance of data to support the categorization of subtypes with subsequent directed therapy toward those unique characteristics. In fact, the use of hormonal therapy for breast cancer is an example of one of the earliest uses of targeted therapy for cancer. At the turn of the last century, a Scottish physician, Sir George Beatson reported three women with advanced breast cancer where oophorectomy led to regression of mammary tumors (Beatson, 1896). With this landmark observation, the idea of using hormonal manipulation to treat cancer was initiated. Later trials were able to demonstrate that sensitivity to hormonal manipulation was only seen in tumors that expressed the estrogen-receptor alpha (ER) (De Sombre et al., 1974). With respect to hormonal

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therapy for breast cancer, there are a number of opportunities for the personalization of care. We will first review the determination of hormone receptor content and various assays to determine sensitivity of individual tumors to endocrine therapy. Once a tumor has been defined as having estrogen and/or progesterone receptor (PR) expression, there are number of potential strategies to target the hormonal pathway that can be broadly divided by mechanism of action. Selective estrogen-receptor modulators (SERMs), such as tamoxifen and raloxifene, are mixed agonists/antagonists of the estrogen receptor. In the breast, tamoxifen acts as an antagonist which results in interruption of transcription of estrogen-regulated genes and disruption of the proliferative effects of estrogen in the breast. Fulvestrant, similarly acts at the level of the estrogen receptor, but in contrast to tamoxifen only has antagonist activities because it leads to degradation of the ER protein with loss of ER and subsequent PR expression (DeFriend et al., 1994). There are a number of strategies to produce estrogen deprivation including suppression of ovarian estrogen production in premenopausal women or use of aromatase inhibitors in postmenopausal women. Finally high dose steroids including estrogen or progesterone can paradoxically also have anti-breast cancer effect. The selection of hormonal therapy is typically based on a number of factors including menopausal status and side effect profile.

2. Assessment of target

As the responsiveness of breast cancer to endocrine therapy is determined by the presence or absence of the ER or PR, an initial challenge is the assessment of hormone receptor status. Initially, this was performed using ligand binding assays (LBAs). The problems with this technique included the need for fresh tissue to perform the assay, the use of radioactive reagents, and lack of sensitivity and specificity in samples with low cellularity (Harvey et al., 1999). Today, ER expression is ascertained via immunohistochemistry (IHC) on paraffin-embedded tumor blocks which overcomes many of the shortcomings of the LBAs including a better correlation with response to endocrine therapy. IHC for ER and PR involves measurement of binding of a monoclonal antibody for the receptor that produces a quantifiable color signal. There are specific guidelines from the American Society of Clinical Oncology and the College of American Pathologists (ASCO-CAP) for practical aspects of testing including the scoring of results. It is recommended that the percentage/proportion of tumor cells that stain, the intensity of the staining, and the interpretation of the stain as either positive ($\geq$1%), negative ($<$1%) or uninterpretable be reported as component of a standard pathology report. Since 2010, laboratory proficiency testing is in place with the CAP Laboratory Accreditation Program in the US (Hammond et al., 2010).

Historically, a number of different studies looked at the minimum cut-off for ER staining to be considered positive. This number was generally $>$10% staining on IHC based on extrapolation of information from LBAs. However, it has subsequently been shown that even as little as 1% staining can translate into a clinical response (Harvey et al., 1999), and therefore the ASCO-CAP guidelines on ER testing recommend consideration of hormonal therapy in tumors that show at least 1% staining, although oncologists are encouraged to weigh the benefits and risks of therapy in patients with ER positivity between 1 and 10% (Hammond et al., 2010).

The next challenge in assessing potential responsiveness to endocrine therapy is to determine if the expression of the ER leads to molecular activity of estrogen-regulated genes. Initial studies focused on the expression of the PR as a measurement of an intact estrogen-receptor responsive pathway with mixed results (Horwitz and McGuire, 1975; Cui et al., 2005). More recent multiparameter assays are exemplified by one study of Symanns and colleagues who developed an index called the SET index (sensitivity to endocrine therapy) (Symanns et al., 2010). This index includes a number of genes both positively and negatively correlated with the expression of the ER. The investigators were able to show that this index predicts benefit from adjuvant hormonal therapy, but not prognosis of patients who did not receive hormonal therapy.

3. Predicting outcome in ER+ patients

Perou and colleagues were among the first to determine that breast cancers had unique molecular signatures that could be classified by gene expression profiles as determined by microarray (Perou et al., 2000). With some overlap, they determined that the classical division of cancers according to ER staining could be further divided into two distinct ER+ groups: luminal A and luminal B, and three groups that did not typically express ER: basal-like, erb b2, and normal breast like. With the advent of microarray analyses, a number of studies have looked at gene expression to predict outcomes of patients with breast cancer. Van't Veer et al. developed a 70-gene prognosis profile that was able to distinguish good and poor prognosis patients on the basis of these gene expression signatures. Of great clinical relevance, some tumors that were small or lymph node negative displayed a poor prognosis signature, suggesting that molecular profiling had the capacity to be more predictive of recurrence than standard pathologic staging (van't Veer et al., 2002). The authors went on to validate this 70-gene signature in nearly 300 consecutive patients at the Netherlands Cancer Institute (van de Vijver et al., 2002). Approximately half of the patients were axillary lymph node positive, and the majority of the node-positive patients received chemotherapy whereas only a small number of the node-negative patients did. In the group classified as having a poor prognosis by the gene signature, the overall 10 year survival was 54.6%. In contrast the group with a good prognosis signature, this was 94.5%. Of note, there was similar distribution of high risk and low risk signatures within the node-positive and node-negative groups, demonstrating that the gene profile is independent of nodal status. It was also determined that the gene signature was associated with grade, ER status and patient age, but not with tumor size or treatment received. This work has formed the basis for the MammaPrint signature that has been validated in a number of additional data sets (Buyse et al., 2006; Bueno-de-Mesquita et al., 2009) and is commercially available. More recently, this signature has been shown to predict benefit from chemotherapy in a population of patients with 0–3 positive lymph nodes

(Knauer et al., 2010) with little benefit observed with the addition of chemotherapy in the low risk group (breast cancer specific survival of 97% in the endocrine therapy alone group and 99% with addition of chemotherapy), but considerable benefit when chemotherapy was added to the high risk group (breast cancer specific survival of 81% with endocrine therapy and 93% with chemotherapy added to endocrine therapy).

Unfortunately, due to the need for specialized techniques and fresh-frozen tissue, the clinical utility of microarray analysis to select patients who are at a higher risk of recurrence can be limited. The challenge was to devise a test that could be done from paraffin samples and would predict not only risk of recurrence, but benefit from endocrine and chemotherapies. Perhaps one of the most widely used assays used for this purpose is the Oncotype DX assay (Paik et al., 2004). This assay was developed using RT-PCR on paraffin-embedded tumor samples initially evaluating expression of a number of potential candidate genes to identify a panel of 16 cancer-related genes and 5 reference genes that are able to predict recurrence of breast cancer. Paraffin blocks from patients enrolled NSABP B-14 trial in which patients with lymph node negative, ER+ tumors were randomized to tamoxifen or placebo were assessed. Patients were divided into low, intermediate, and high risk groups based on Oncotype recurrence score (RS). In aggregate, patients in the low risk category had a 6.8% risk of recurrence at 10 years, patients in the intermediate risk group had a 14.3% risk of recurrence at 10 years, and those in the high risk group had a 30% risk of recurrence. The risk of recurrence increased continuously with increased recurrence score. The recurrence score was compared to standard risk factors for recurrence such as age and tumor size. It was found that the recurrence score had more predictive power and was independent of either of these variables. Furthermore, the recurrence score was also able to predict response to CMF-based chemotherapy in patients with ER+, node-negative tumors treated on NSABP B-20. Patients with a low recurrence score (RS < 18) derived little to no benefit from chemotherapy (mean absolute decrease in recurrence of -1.1%), whereas patients in the high risk group (RS ≥ 31) derived considerable benefit (mean absolute decrease in recurrence of 27.6%) (Paik et al., 2006). The Oncotype recurrence score has also been evaluated in postmenopausal women with ER+, node-positive tumors and was also able to predict a high risk group in whom chemotherapy was beneficial, as well as a group in which chemotherapy added little benefit to endocrine therapy (Albain et al., 2010). Currently, both the NCCN and St. Gallen International Breast Cancer Expert panels recommend the use of Oncotype Dx to guide decisions for adjuvant chemotherapy in ER+ women (Goldhirsch et al., 2011; NCCN, 2011).

The current clinical questions include prospective validation of the Oncotype recurrence score to determine the benefit of chemotherapy in the intermediate risk groups (RS 18–31) which was not clear in the previously mentioned trials. Also needed is an analysis of recurrence score in the context of more contemporaneous chemotherapies such as taxanes, and endocrine therapies such as aromatase inhibitors. The National Cancer Institute (NCI) sponsored, TAILORx trial (Phase III randomized study of adjuvant combination chemotherapy and hormonal therapy versus adjuvant hormonal therapy alone in women with previously resected axillary node-negative breast cancer with various levels of risk for recurrence, NCT00310180) has been designed to answer these questions. In this study, in which all major American cooperative groups participated, nearly 9000 patients were enrolled and accrual is complete. Importantly, patients with recurrence score of 11–25 are randomized to receive endocrine therapy alone or chemotherapy followed by endocrine therapy. The primary objective is to assess noninferiority of endocrine therapy alone compared with the combination. An additional study is now evaluating the use of Oncotype in postmenopausal women with intermediate risk HR-positive, node-positive breast cancer (NCT01272037). Similarly, a large prospective evaluation of the MammaPrint assay is being evaluated primarily in Europe. This trial, entitled the MINDACT trial (Microarray in node-negative disease may avoid chemotherapy) is being conducted by the European Organization for Research and Treatment of Cancer (EORTC) and the TRANSBIG research consortium.

Ongoing research is evaluating additional prognostic assays. Examples include the use of two predictive gene expression indices , the HOXB13: IL17BR (H:I) and the molecular grade index (MGI) which has been found to correlate with prognosis in ER+ patients with early stage breast cancer (Jerevall et al., 2011; Ma et al., 2004). The Mammastrat test has identified additional markers predictive of outcome which can be assessed using immunohistochemistry, and therefore has the potential to be more broadly performed in hospital laboratories (Ross et al., 2008; Bartlett et al., 2010) At this time; none of these assays is clearly superior over the other by any measure evaluated including cost-effectiveness (Retel et al., 2011).

4. Treatment of premenopausal women

Although the very first explorations of endocrine therapy for breast cancer involved the use of ovarian suppression in premenopausal women by Dr. Beatson, for much of the last century, the choice of endocrine therapy for women with breast cancer did not discriminate by menopausal status. With the observations of different outcomes in pre- and postmenopausal women, as well as advent of therapies like aromatase inhibitors, which are felt to be effective only in postmenopausal women, current treatment for hormonal driven breast cancers varies depending on menopausal status. In premenopausal women, two major strategies exist for hormonal therapy: ovarian suppression/ablation and selective estrogen-receptor modulators (SERMs), of which tamoxifen is most well studied. Here, the focus will be on adjuvant therapy which is more highly nuanced than in the advanced setting.

5. Ovarian suppression

Ovarian ablative strategies as a therapy for premenopausal women with ER+ breast cancer are achieved via either surgical removal of the ovaries or directed radiation therapy to the ovaries. Suppressive strategies can also be used via the administration of LHRH analogs. These strategies are generally

felt to be equivalent for efficacy, as demonstrated in a small study in patients with advanced disease (Taylor et al., 1998). The major difference between medical or surgical ovarian suppression is the reversibility. LHRH agonists act via disruption of the hypothalamic–pituitary–ovarian axis and ultimately result in downregulation of pituitary LHRH receptors (Limonta et al., 2001). After administration of LHRH agonists, of which goserelin, triptorelin, and leuprolide are most commonly used, estrogen and gonadotropin levels fall to postmenopausal range (Harvey et al., 1985). These agents need to be continuously administered as, once they are stopped, the normal axis recovers. In contrast, surgical approaches are permanent, but advantages include reduction of risk of ovarian cancer if an individual harbors a deleterious mutation in *BRCA1/2* and eventual cost and time savings as compared to need for continued administration of LHRH agonists.

Studies evaluating ovarian suppression have examined its use in three major contexts, alone, with other hormonal therapies, or in addition to or instead of chemotherapy. Ovarian suppression alone, while historically important, is used less currently due to the widespread use of chemotherapy and tamoxifen. However in the 1995 EBCTCG meta-analysis, ovarian suppression clearly improves the risk of recurrence and death by 25% and 24%, respectively when used in the adjuvant setting compared to no additional therapy (EBCTCG, 1996). The most recent EBCTCG update in 2005 again showed similar benefit from ovarian suppression with similar improvements seen in both younger and older premenopausal women (<40 year old age group: 25% reduction in recurrence and 29% reduction in mortality; 40–49 year old group: 29% reduction in recurrence and mortality) (EBCTCG, 2005).

One of the potential age- and dose-dependent effects of chemotherapy is ovarian toxicity and resultant early menopause in many women. Thus it was postulated that adjuvant chemotherapy might actually function via ovarian suppression. In the studies that examined ovarian suppression alone compared to chemotherapy alone, the outcomes were similar and there was not a clear superiority for either strategy (Kaufmann et al., 2003, 2007; Ejlertsen et al., 2006; Thomson et al., 2002; Schmid et al., 2007; IBCSG, 2003; von Minckwitz et al., 2006; Jonat et al., 2002). The only clear advantage to CMF chemotherapy over ovarian suppression is in hormone receptor-negative cases (Kaufmann et al., 2003). Potential limitations include that many of the studies evaluating chemotherapy versus ovarian suppression used older chemotherapy regimens such as CMF (cyclophosphamide, methotrexate, 5-FU) and do not reflect more modern standards like anthracyclines, taxanes, and trastuzumab. Moreover, many of the older studies did not require tumors to be ER+.

The administration of ovarian suppression after chemotherapy has not consistently resulted in additional benefit, again likely secondary to the fact that chemotherapy itself results in ovarian suppression for many patients. The trials that have examined this, in aggregate, do not show any advantage in recurrence or survival. But it is important to note that in subset analysis of women who are not likely to become postmenopausal with chemotherapy, the addition of ovarian suppression, in fact, has been demonstrated to improve outcomes. In the IBCSG VII trial (IBCSG, 2003), women ≤ 39 years old who were ER+ had a relative risk for disease-free survival of 0.34 ($P = 0.02$) DFS favoring the addition of goserelin to CMF alone; although interestingly a similar relative risk (0.34) was seen when goserelin alone was compared to CMF plus goserelin ($P = 0.02$) in the IBCSG VIII trial. There was no additional benefit to adding goserelin to CMF in women who were ER+ and ≥ 40 as well as in the population as a whole, including ER+ and ER− women. Similar results were also reported by Arriagada et al. who found in women who were <40 and ER+ that the addition of ovarian suppression after FAC/FEC (5-fluorouracil, doxorubicin or epirubicin, and cyclophosphamide) or CMF-based chemotherapies was beneficial (Arriagada et al., 2005). The Intergroup study, INT 0101/E5188, did not show an improvement with the addition of goserelin to CAF, although there was a trend toward benefit again in women < 40 (Davidson et al., 2005). The addition of ovarian suppression to chemotherapy may become a more relevant approach with increasing use of anthracycline and taxane regimens which tend to be less toxic to the ovaries than CMF (Stearns et al., 2006).

With the demonstration of benefit with tamoxifen in premenopausal women, the next generation of adjuvant trials examined the addition of tamoxifen to ovarian suppression as compared to chemotherapy. Unfortunately none of the studies evaluated the important question of tamoxifen alone, ovarian suppression alone, or both with and without chemotherapy. The available data does suggest that the use of combined endocrine therapy is at least as efficacious as or more efficacious than chemotherapy alone in some patient populations. The ABCSG-5 study compared CMF to goserelin with tamoxifen in over 1000 premenopausal women with ER and/or PR+ breast cancer. The use of ovarian suppression plus tamoxifen was found to be superior to CMF in regards to relapse-free survival (RR 1.4) with a trend toward improved overall survival (Jakesz et al., 2002) The Italian group similarly examined CMF versus ovarian suppression and tamoxifen, with no difference seen in disease-free and overall survival between the two strategies (Boccardo et al., 2000). Two smaller French studies also demonstrated equivalence between these two treatment strategies (Roche et al., 1996, 2006). The International Breast Cancer Study Group demonstrated equivalence between anthracycline-based chemotherapy and ovarian suppression plus tamoxifen in a node positive, ER+ population in regards to disease-free and overall survival; however this study was closed prematurely for slow accrual (Thurlimann et al., 2009). In addition a meta-analysis of ovarian suppression added to any therapy whether tamoxifen alone, chemotherapy alone, or both showed significant benefit to the addition of ovarian suppression in premenopausal women in terms of both recurrence (12.7%, $P = 0.02$) and survival (15.1%, $P = 0.03$) (Cuzick et al., 2007). Table 1 summarizes key trials evaluating ovarian suppression.

Contemporary questions about the role of ovarian suppression include assessment of benefit of ovarian suppression with tamoxifen compared to tamoxifen alone with and without chemotherapy that includes an anthracycline and/or taxane. These questions will be answered in ongoing trials. The SOFT trial randomized women who remain premenopausal after chemotherapy or who do not receive chemotherapy to one of three options: tamoxifen alone, ovarian suppression plus tamoxifen, or ovarian suppression plus the aromatase

Table 1 – Summary of selected adjuvant hormonal therapy studies with ovarian suppression.

Intervention	Trial	Patient characteristics	Regimen	Benefit	Notes
Ovarian suppression (OS)	IBCSG VIII (IBCSG, 2003)	N = 1063 Pre- or peri ER+/− Node (−)	CMF × 6 (oral) vs. Goserelin vs. CMF × 6 → Goserelin	For ER+: CMF → G vs. CMF: RR for DFS 0.80, P = 0.26	In ER+ group as whole, no difference between 3 treatment arms; If ER+ and ≤39 years old: 5 year DFS: Goserelin 62% CMF 64% CMF → Goserelin 85% (P = 0.02)
	INT 0101 (Davidson et al., 2005)	N = 1503 Premenopausal Node (+) ER and/or PR+	CAF vs. CAF-Z vs. CAF-ZT	CAF-Z vs. CAF: HR for DFS 0.93, P = 0.22 HR for survival 0.88, P = 0.14 CAF-ZT vs. CAF-Z: HR for DFS 0.74, P = <0.01 HR for survival 0.91, P = 0.21	Trend toward benefit with ovarian suppression after chemo if <40 years
	Arriagada et al., 2005	N = 926 Premenopausal ER/PR+ or − Grade II/III or node (+)	Chemo (FAC, FEC, or CMF) vs. Chemo + OS	For all patients: RR for recurrence or death 1.1, P = 0.51 RR for death 1.2, P = 0.19 For ER+ and <40 years: RR recurrence or death 0.49, P = 0.005	Benefit to ovarian suppression after chemo only if ER+ and <50
	EBCTCG, 2005	N = 7601 Age < 50 at diagnosis 47% ER unknown 61% node+	Ovarian suppression by surgery, XRT, or LHRH inhibitor	Benefit on recurrence 15-year gain 4.3% HR 0.83 favoring Ovarian suppression Benefit on breast cancer mortality 15-year gain 3.2% HR 0.87 favoring OS	Benefit in node (+) and (−) More benefit if no chemo given Numbers too small for other subgroup analysis

inhibitor, exemestane. This trial has finished accrual and results are anticipated. The TEXT trial similarly evaluates ovarian suppression with tamoxifen or exemestane, with chemotherapy allowed at the discretion of the treating physician. Unfortunately, the PERCHE trial which evaluated the need for chemotherapy in patients who received ovarian suppression with tamoxifen or exemestane was closed for poor accrual in 2006. Currently in the United States, tamoxifen alone is generally recommended for premenopausal, ER+ women with or without chemotherapy depending on Oncotype Dx recurrence score and nodal involvement. The addition of ovarian suppression is category 2B (recommendation based on lower level evidence and there is no uniform NCCN consensus) in the NCCN guidelines. The St. Gallen International Expert Consensus Panel also felt that tamoxifen alone or ovarian suppression plus tamoxifen were acceptable, with a preference for tamoxifen alone (Goldhirsch et al., 2011). Recently the American Society of Clinical Oncology (ASCO) has adapted the practice guidelines of Cancer Care Ontario regarding the use of ovarian suppression (Griggs et al., 2011). These guidelines essentially state that ovarian suppression has less role in the setting of anthracycline- and taxane-based chemotherapy regimens and tamoxifen, but may play a role when either or both of these agents are unable to be used due to side effects or patient preference.

6. Tamoxifen

While tamoxifen is currently used in both pre- and postmenopausal women, early meta-analyses initially showed little benefit with tamoxifen in premenopausal women which subsequently shifted the focus to ovarian suppressive strategies as discussed above (EBCTCG, 1992).The later Early Breast Cancer Trialists Collaborative Group (EBCTCG) overview and meta-analysis of 194 randomized trials employing adjuvant chemotherapy and endocrine therapy demonstrated the 15-year breast cancer recurrence rate was reduced from 45% to 33% with use of tamoxifen, and also showed a 41% reduction in annual recurrence rate and reduction of breast cancer mortality by 35%. This meta-analysis determined that the risk reduction with tamoxifen was significant in both pre- and postmenopausal women and was independent of the receipt of chemotherapy (EBCTCG, 2005). The 2011 EBCTCG overview of 20 trials evaluating tamoxifen compared to no tamoxifen demonstrated significant reductions in recurrence during

the initial 10 years following commencement of treatment and improvements in mortality seen through 15 years (EBCTCG, 2011). Based on these results and those of landmark trials, like NSABP B-9, B-14 and B-20, the use of tamoxifen as hormonal therapy is currently a standard of care, particularly in premenopausal women, with or without chemotherapy. Tamoxifen has been evaluated in clinical trials compared to no additional treatment, compared to chemotherapy, and in combination with chemotherapy.

Early studies with tamoxifen evaluated its use as compared to no additional adjuvant therapy and demonstrated significant improvements in outcome with the addition of tamoxifen regardless of menopausal status (Fisher et al., 1989, 1996; Scottish, 1987; Stewart et al., 2001). The use of tamoxifen resulted in an improvement in disease-free survival to 83% from 77% with placebo in pre- and postmenopausal women with tumors that were ER+ and node negative in NSABP B-14. Later updates demonstrated a survival advantage as well, with 80% overall survival in the tamoxifen treated group compared to 76% in those treated on placebo ($P = 0.02$). These studies of tamoxifen versus placebo provided the clearest delineation of side effects on tamoxifen. In patients on NSABP B-14 who received placebo, 55% of women had a grade 1 or 2 toxicity, with 3% having a grade 3 or 4 Toxicity. In the tamoxifen treated arm, 60% had grade 1 or 2 toxicity and 5% had a grade 3 or 4 adverse event. The toxicities that were significantly more frequent in the tamoxifen arm were hot flashes, menstrual irregularities, and vaginal discharge. The serious adverse events attributed to tamoxifen with more frequency than placebo were endometrial cancer and thromboembolic events. The total thromboembolic event rate, including deep venous thrombosis and stroke, was 0.4% in those on placebo, but 1.7% in those treated with tamoxifen. It is important to note that these events were seen almost exclusively in women >60 years. The number of observed uterine cancers was 21 in the tamoxifen arm and 3 in the placebo arm. These data and others suggest that tamoxifen is generally safe and well-tolerated in the majority of patients, particularly those who are premenopausal.

As summarized above with respect to ovarian suppression alone, the next question about tamoxifen is its efficacy as compared to chemotherapy. Two studies have evaluated this. The Italian GROCTA study, compared tamoxifen to chemotherapy (CMF/epirubicin) alone and to chemotherapy with tamoxifen (Boccardo et al., 1992). Tamoxifen was more effective than CMF/epirubicin chemotherapy in postmenopausal women and as effective as chemotherapy in premenopausal women. The addition of CMF/epirubicin chemotherapy to tamoxifen did not improve the outcomes seen with tamoxifen alone, except in a small subset of premenopausal women with ≥4 positive lymph nodes. The GABG trial randomized low risk women (ER/PR+, 1–3 + nodes) to CMF or tamoxifen; whereas high risk women (>4 nodes +, or 1–3 nodes + and ER/PR-negative) were randomized to AC alone or AC plus tamoxifen. Similar to the GROCTA study, the GABG study showed that tamoxifen had greater efficacy than CMF in low risk, postmenopausal women. In premenopausal women, however, chemotherapy appeared to be more beneficial than tamoxifen in low risk women, and tamoxifen added to AC did not enhance benefit in high risk women. It is difficult to place these results in the context of treating ER+, premenopausal women as less than half of the women in that population had ER+ tumors (Kaufmann et al., 1992, 2005).

A number of additional studies evaluated the benefit of adding tamoxifen to chemotherapy as compared to chemotherapy alone. Despite the heterogeneity in the trials with respect to durations of both chemotherapy and hormonal therapy and types of therapy used, in aggregate, and later corroborated by the EBCTCG meta-analysis, tamoxifen improved the risk of recurrence and death over chemotherapy alone (EBCTCG, 2005). These studies also confirmed the logical conclusion that tamoxifen only benefits those with ER+ tumors and there is no benefit to the use of tamoxifen to ER− individuals, which likely diluted the effects of tamoxifen in many of the early studies. For example, the MA.12 trial (Bramwell et al., 2010) evaluated AC or CMF-based chemotherapy followed by either placebo or tamoxifen in premenopausal women, including both node positive and node negative and ER+ and ER-negative cases. Tamoxifen led to significant improvement in disease-free survival with a hazard ratio of 0.77 ($P = 0.056$) and a non-significant improvement in overall survival (HR 0.78, $P = 0.12$). Likewise, the European Organisation for Research and Treatment of Cancer Breast group trial demonstrated that tamoxifen improved the risk of recurrence after CMF or anthracycline-based chemotherapy in women with stages I–IIIA breast cancer (recurrence-free survival 73% with tamoxifen vs. 67% on control, $P = 0.035$). The greatest benefits were seen in women whose tumors were ER+ with nodal involvement (Morales et al., 2007). The International Breast Cancer Study Group trial 13–93 evaluated the addition of tamoxifen specifically in node+, premenopausal patients and showed that tamoxifen greatly improved disease-free survival in the ER+ (HR 0.59, $P < 0.0001$), but not in the ER-negative cohort (IBCSG, 2006). Similarly, in a node negative only population in the Intergroup Protocol (INT-0102), tamoxifen also improved disease-free (HR = 1.32; $P = 0.003$) and overall survival (HR = 1.26; $P = 0.03$)in the subset of CMF or CAF treated patients with ER+ disease , and had no effect on ER-negative cases (Hutchins et al., 2005). Selected trials with tamoxifen are summarized in Table 2.

Premenopausal females with hormone sensitive breast cancer should be treated with a 20 mg dose of tamoxifen for five years. Studies comparing shorter durations of tamoxifen to 5 years support its use for 5 years (Belfiglio et al., 2005; Stewart et al., 2001; Delozier et al., 2000). There is no published evidence that a longer treatment trial is beneficial, and it may be detrimental as seen in both the Scottish trial and NSABP B-14 that had cohorts randomized to tamoxifen durations greater than 5 years (Fisher et al., 2001; Stewart et al., 2001; Tormey et al., 1996). Two ongoing studies are examining the question of tamoxifen duration combined in over 20,000 patients. In contrast to the NSABP and Scottish trials, these trials, Adjuvant Tamoxifen-Treatment-Longer against Shorter (ATLAS) and Adjuvant Tamoxifen Treatment-Offer More (aTTom), have presented preliminary data with disease-free survival benefit to longer tamoxifen durations (Peto, 2007; Gray et al., 2008). Although there were twice as many

Table 2 – Summary of selected adjuvant hormonal therapy studies with tamoxifen.

Intervention	Trial	Patient characteristics	Regimen	Benefit	Notes
Tamoxifen	ABCSG-5 (Jakesz et al., 2002)	N = 1034	CMF × 6 (iv) vs. Goserelin × 3 years plus Tam × 5 years	Premenopausal ER and/or PR+ Stage I or II	RR for relapse: 1.4 favoring hormonal treatment, $P = 0.037$ RR for OS: not significant, $P = 0.195$
	IBCSG 13–93 (IBCSG, 2006)	N = 1246 Premenopausal Node + ER+ or −	Chemo (AC/EC × 4 → CMF × 3) vs. Chemo + Tam	For ER+: HR for DFS 0.59, $P < 0.0001$ HR for survival 0.86, $P = 0.36$ For ER−: HR for DFS 1.02, $P = 0.89$ HR for survival 0.92, $P = 0.63$	Benefit in DFS only if ER+ with Tam after chemo
	NSABP B-14 (Fisher et al., 1996)	N = 2818 ER+ Node (−)	Tam vs. Placebo	10 year follow-up DFS: RR = 0.66 favoring Tam OS: RR = 0.84 Favoring Tam	Advantage found to discontinue Tam after 5 years; Detriment to disease-free survival for >5 years Tam
	EORTC (Morales et al., 2007)	N = 1724 Pre- and postmenopausal Stages I–IIIA ER/PR+ or −	CMF or anthracycline vs. chemo → Tam	For all patients: HR for RFS favoring Tam 0.84, $P = 0.0349$ HR for OS 0.97, $P = 0.7377$	For ER/PR+: 5-year RFS on Tam 77%, 70% control, $P = 0.014$
	EBCTCG, 2011	N = 21,712 All studies with duration of Tam at least 2–3 years		Benefit to Tam in reduction of risk of recurrence: RR = 0.53 Benefit in survival: RR = 0.71	Benefit to tamoxifen seen in weakly ER+, but not ER− Benefit to tam is independent of: Age, nodes, tumor grade or size, and use of chemotherapy

instances of endometrial cancer in the longer duration of tamoxifen group in the aTTom trial, there were no increases in death related to endometrial cancer.

The efficacy of tamoxifen is dependent on treatment compliance and potential for resistance. Despite the great benefit to tamoxifen as described above, approximately one-third of women treated with adjuvant hormonal therapy will have a recurrence of their cancer. Young women in particular, may be more susceptible to resistance (Ahn et al., 2007) A number of factors contribute to resistance including loss of or variable expression of the ER, post-translational modifications of the ER such as methylation or phosphorylation, alterations in ER-associated transcription factors and co-activators, and various mechanisms involving other growth factor receptors and signaling pathways including EGRF, IGF1R, MAPK and PI3K signaling (Ring and Dowsett, 2004) In fact, in large data sets, it has been shown that tumors that are ER+, but PR− and overexpress HER-1 or HER-2, demonstrate worse disease-free survival on tamoxifen (Arpino et al., 2005) In addition, variable CYP2D6 activity, which is further discussed below, may contribute to an individual's resistance to tamoxifen. At the present time, there are no tests to evaluate prospectively for emerging endocrine resistance and most mechanisms of resistance have been studied in *in vitro* as opposed to *in vivo* settings.

7. Treatment of postmenopausal women: aromatase inhibitors

Tamoxifen has shown benefit to women with ER+ breast cancers irrespective of menopausal status. However, a proportion of patients will have recurrences despite tamoxifen. In the past 10 years, a number of studies evaluating the use of aromatase inhibitors as an alternative to tamoxifen were undertaken after studies in the metastatic setting showed considerable benefit to these agents. In contrast to tamoxifen which acts at the level of the ER, aromatase inhibitors act by preventing the peripheral conversion of androgens to estrogens by blocking the aromatase enzyme and result in subsequent decline in estradiol levels. As such, aromatase inhibitors are not active in women with functioning ovaries and may in fact lead to higher estrogen levels when used in premenopausal women. This occurs because of reflex increased gonadotropin secretion after the initial decline in estradiol levels which subsequently leads to increased ovarian hormonal secretion (Smith and Dowsett, 2003). In postmenopausal women these agents offer the advantage of modestly improved activity over tamoxifen, and because of lack of agonist activity these agents do not possess the same thrombotic or endometrial cancer risks. The three currently used

aromatase inhibitors in the adjuvant setting are anastrazole, letrozole, and exemestane. A number of large, multi-center studies have evaluated the aromatase inhibitors in three major adjuvant clinical settings: 1 instead of 5 years of tamoxifen, 2 after 2–3 years of tamoxifen and 3 after the completion of 5 years of tamoxifen. The major aromatase inhibitors are summarized in Table 3.

The ATAC trial (Anastrazole, Tamoxifen, Alone or in Combination) randomized postmenopausal women with early stage breast cancer to five years of anastrazole, tamoxifen, or both agents. The initial results demonstrated improvement in disease-free survival at 3 years compared to tamoxifen or the combination treatment (HR 0.83, $P = 0.013$) The most recent update with 10 years of follow-up confirms significant improvements in disease-free survival (HR 0.91, $P = 0.04$), time to recurrence (HR 0.84, $P = 0.001$), incidence of new contralateral breast cancer (HR 0.68, $P = 0.01$) and time to distant recurrence (HR 0.87, $P = 0.03$) favoring anastrazole. Importantly, the adverse events of concern with tamoxifen such as thromboembolic events or endometrial cancer were not observed with anastrazole. The aromatase inhibitor did cause more arthralgias, myalgias, osteoporosis and fractures than tamoxifen. This is not surprising as tamoxifen in postmenopausal women, like its related SERM, raloxifene, which is specifically marketed for osteoporosis prevention, is protective against bone loss due to its mixed agonist effect on bone. However, once the active treatment finished, the fracture rates became more similar with time (Baum et al., 2002; Forbes et al., 2008; Cuzick et al., 2010).

Another aromatase inhibitor, letrozole, was also compared to tamoxifen in postmenopausal women in the adjuvant setting in the BIG 1–98 trial. In this trial a switching strategy from letrozole to tamoxifen or vice versa was also evaluated. Initial reports revealed that treatment with letrozole significantly improved disease-free survival (HR 0.81, $P = 0.003$) after a median follow-up of 2 years (Thurliman et al., 2005). Side effects were similar to those described with anastrazole. The most recent update of this study in 2011 demonstrated that 5 years of letrozole compared 5 years of tamoxifen monotherapy resulted in a survival advantage (HR 0.79), which is the first survival advantage to be demonstrated with AI monotherapy. Also the comparison of switching from letrozole to tamoxifen or vice versa was not significantly different compared to letrozole monotherapy (Regan et al., 2011). Of interest, the incidence of fracture was similar in the group initially treated with tamoxifen and later switched to letrozole (9.4% fracture incidence) as compared to the group assigned to letrozole monotherapy (9.8% fracture incidence). In contrast, the group randomized to tamoxifen monotherapy had a fracture incidence of 7.3% which was comparable to the cohort treated with letrozole then switched to tamoxifen (7.5%) (Mouridsen et al., 2009).

The IES trial evaluated switching to the steroidal aromastase inhibitor, exemestane, after 2–3 years of tamoxifen to the completion of 5 years of tamoxifen. Again, benefit was seen favoring the aromatase inhibitor arm with a 24% improvement in disease-free survival (Coombes et al., 2007). When patients who were estrogen-receptor negative were

Table 3 – Summary of major aromatase inhibitor trials.

Trial	Population	Intervention	Results
ATAC (Arimidex, Taxomifen, Alone or in Combination) (Cuzick et al., 2010)	$N = 6241$ 10 year follow-up	Tamoxifen vs. Anastrazole	ER+: favoring anastrazole HR for DFS: 0.86, $P = 0.003$ HR for TTR: 0.79, $P = 0.0002$ HR for TTDR: 0.85, $P = 0.02$ HR for CLBC: 0.62, $P = 0.003$ No effect for OS
BIG 1–98 (Regan et al., 2011)	$N = 4922$ 8.1 years follow-up	Letrozole vs. Tamoxifen vs. Switch from Letrozole to Tam vs. Switch from Tam to letrozole	All Patients: Let vs. Tam ITT HR for DFS: 0.86, $P = 0.007$ HR for OS: 0.87, $P = 0.048$ HR for DRFI: 0.86, $P = 0.047$ HR for BCRI: 0.86, $P = 0.03$ DFS: no different with either switch compared to letrozole alone
IES (Intergroup Exemestane Study) (Coombes et al., 2007)	$N = 4724$ 55 month follow-up	After 2–3 years of Tam: Randomized to continue with tam vs. switch to exemestane	ITT: Favoring exemestane: HR for DFS: 0.76, $P = 0.0001$ HR for OS: 0.85, $P = 0.08$ HR for TTDR: 0.83, $P = 0.03$
MA.17 (Goss et al., 2008)	$N = 5187$ 5.3 year follow-up	Letrozole vs. Placebo after 5 years of Tamoxifen	Favoring letrozole: HR for DFS: 0.37, $P < 0.0001$ HR for DDFS: 0.38, $P = 0.004$ HR for OS: 0.30, $P < 0.0001$ HR for CLBC: 0.18, $P = 0.004$

N = number, CMF: cyclophosphamide, methotrexate, 5-FU, G = goserelin, CAF = cyclophosphamide, Adriamycin, 5-FU, Z = zoladex, T = tamoxifen, FEC = 5-FU, epirubicin, cyclophosphamide, FAC = 5-FU, adriamycin, cyclophosphamide, XRT = radiation, HR = hazard ratio, DFS = disease-free survival, TTR = time to recurrence, TTDR = time to distant recurrence, CLBC = contralateral breast cancer, OS = overall survival, ITT = intent to treat, DRFI = distant recurrence-free interval, BCRI = breast cancer-free interval.

excluded, there was also an improvement seen in overall survival (HR = 0.83, $P = 0.05$). Exemestane was also evaluated as upfront monotherapy compared to sequential tamoxifen followed by exemestane. The approaches yielded identical results with 5 year disease-free survival of 85% in the sequential group and 86% in the single agent exemestane arm (van de Velde et al., 2011).

The use of letrozole also resulted in improved outcomes when patients were treated with 5 years of letrozole after completion of 5 years of tamoxifen. The MA.17 trial randomized postmenopausal, node-positive and node-negative women who had completed 4.5–6 years of tamoxifen to an additional 5 years of letrozole or placebo. After 30 months, there was a significant benefit seen in women randomized to letrozole in terms of disease-free survival (HR = 0.58, $P < 0.001$) and distant disease-free survival (HR = 0.60, P 0.002). In the subset of patients who were node positive, there was a significant improvement seen in overall survival as well (HR = 0.61, $P = 0.04$). Generally the therapy was well-tolerated, and the incidence of fracture was the same in each arm, suggesting that the risk of fracture seen in the above studies when compared to tamoxifen reflected the anti-osteopenic effects of tamoxifen (Goss et al., 2005, 2008). When adjusted for cross-over that occurred after unblinding, there was also a significant improvement in overall survival observed in the entire population (HR 0.61, $P < 0.001$) (Jin et al., 2011)

The EBCTCG has evaluated the use of aromatase inhibitors as compared to tamoxifen in a recent meta-analysis involving 19,000 patients. As was seen in the individual studies the use of an aromatase inhibitor whether upfront or sequentially with tamoxifen results in significantly reduced risk of recurrence, with absolute benefit of approximately 3%. Additionally, in the group of patients who switched from tamoxifen to an aromatase inhibitor, there was a significant improvement in deaths from breast cancer (absolute decrease 0.7%, $P = 0.02$) (Dowsett et al., 2010). Current guidelines suggest that most postmenopausal women with hormone receptor-positive breast cancer consider should incorporate an aromatase inhibitor therapy at some point during adjuvant treatment, either as upfront therapy or as sequential treatment after tamoxifen (ASCO guidelines). After careful consideration of side effect profiles and patient preferences, options for postmenopausal women include treatment with AIs either as initial management for five years, or sequential therapy following 2–3 years use of tamoxifen, or as extended therapy following 5 years of tamoxifen (Burstein et al., 2010). The optimal timing and duration of endocrine treatment remain unresolved. Recent studies have examined whether there is an optimal AI. The American College of Surgeons Oncology Group (ACOSOG) Z1031 phase II trial randomized patients to neo-adjuvant letrozole, anastrazole, or exemestane. The clinical response rates were 62.9%, 74.8% and 69.1% with exemestane, letrozole, and anastrazole respectively. The prespecified statistical analysis resulted in selection of anastrazole and letrozole for further study in the neo-adjuvant setting, although it is important to note that complete responses seen with exemestane (21.8%) were as frequent as those with letrozole (21.3%) and numerically higher than those with anastrazole (17.9%). Additionally, all three agents were found to have equivalent biological activity in terms of changes in Ki67 and the PEPI score (Preoperative Endocrine Prognostic Index, a measure of response to neo-adjuvant hormonal therapy) post-treatment and comparable toxicity (Ellis et al., 2011).

While it is undeniable that aromatase inhibitors reduce the risk of breast cancer recurrence when compared to tamoxifen, the survival advantage with this class of drugs has only recently emerged when given as monotherapy or in a switch strategy (Gelber et al., 2011). It is important that clinicians not only take into account the breast cancer risks, but also the overall health of the patient, specifically with respect to osteoporosis, hyperlipidemia, cardiovascular risks , as well as the risks of endometrial cancer and thromboembolic events. A recent meta-analysis by Amir et al. examined the adverse events associated with both AIs and tamoxifen to evaluate why no overall survival advantage is seen with aromatase inhibitors, despite improvement in recurrence and disease-free survival (Amir et al., 2011). The authors found that aromatase inhibitor monotherapy resulted in a non-significant increase in the odds of death without breast cancer recurrence, although the number needed to harm was high at 610, with a difference in absolute risk of 0.2%. The investigators found that treatment with a switching strategy resulted in a significant reduction in the odds of death without recurrence (OR = 0.87, $P = 0.03$) compared to tamoxifen or AI monotherapy. A model that incorporates an individual patient's cardiovascular and other risks with the risk of recurrence from their breast cancer is needed and would assist clinicians in personalizing therapy (Puhalla et al., 2011).

8. Overcoming resistance to aromatase inhibitors: emerging data

Despite, the strong efficacy of aromatase inhibitors in the adjuvant setting, a subset of patients will go on to develop later recurrence. A number of strategies are under investigation to reverse this resistance to anti-estrogen therapy. One such strategy is targeting the mammalian target of rapamycin (mTOR) pathway. The mTOR and ER pathways are intertwined, and endocrine resistance has been associated with abnormal signaling through the mTOR pathway. Baselga and colleagues recently reported the results of a phase III randomized trial of exemestane plus placebo compared to exemestane plus everolimus, which inhibits mTOR in patients who had progressed after non-steroidal aromatase inhibitor therapy in either the adjuvant or metastatic setting (Baselga et al., 2011). In this study, median progression-free survival was significantly improved with the addition of everolimus compared to exemestane alone (6.9 months vs. 2.8 months, HR 0.43, $P < 0.001$). Similar improvements have also been described in the neo-adjuvant setting and in combination with tamoxifen, confirming that targeting the mTOR pathway is an important strategy in either treatment of resistant disease or upfront (Baselga et al., 2009; Bachelot et al., 2010).

9. Fulvestrant

Fulvestrant is a selective estrogen-receptor degrading agent that, unlike tamoxifen, does not possess any agonist activity.

It is currently indicated for the treatment of postmenopausal women with ER+, metastatic breast cancer after failure of a non-steroidal aromatase inhibitor. Theoretically fulvestrant should be active in pre- and postmenopausal women but, the drug has only been tested in women who are postmenopausal, and its use is generally limited to that setting.

Fulvestrant has been compared in a large randomized clinical trial to the steroidal AI, exemestane after the failure of a non-steroidal AI. It was demonstrated that both options have activity in this setting, and the efficacy was similar with both fulvestrant and exemsetane. The clinical benefit rate was just over 30% with either agent (Chia et al., 2008). It is of mention that fulvestrant has been demonstrated to have greater efficacy when administered with a loading dose and at higher dose (Pritchard et al., 2010).

10. Therapeutic use of estrogens and progesterones

Prior to the advent of agents such as tamoxifen or aromatase inhibitors, commonly used therapies for breast cancer included the use of high doses of estrogen or progesterone. These approaches are generally more poorly tolerated than SERMs or AIs, but nonetheless remain an option for patients with refractory, metastatic disease. Agents with activity include estradiol and megestrol acetate. Megestrol acetate has been shown to have response rates of approximately 25% with risks of weight gain and thrombotic events (Abrams et al., 1999). Estradiol has been evaluated at lower (6 mg daily) and higher doses (30 mg daily), with similar efficacy (clinical benefit rate 28% at high dose and 29% at low dose) and greater tolerability at the lower dose (Ellis et al., 2009). These therapies remain an option in the treatment of patients with ER+ breast metastatic cancer, although they are typically used after failure of agents like AIs, tamoxifen, and fulvestrant due to the better tolerability of those agents.

11. Clinical challenges: compliance

Despite, the extensive amount of data supporting the use of endocrine therapy in women with breast cancer, non-adherence to therapy is a major concern. One study showed that only half of women prescribed tamoxifen finished the recommended five years of treatment (Partridge et al., 2003). Similar rates of discontinuation have been observed with aromatase inhibitors as well (Hershman et al., 2010). In countries with nationalized healthcare systems, and therefore without economic barriers to adherence, non-compliance rates are still high. In a recent study presented by authors in British Columbia, Canada non-adherence rates as defined by <80% of eligible prescription days filled were as high as 41% for tamoxifen and 37% for AIs (Chan et al., 2009). Similarly, a study evaluating non-compliance with aromatase inhibitors in the Kaiser Permanente system revealed that approximately one-third of patients discontinued hormonal therapy early and another third were non-adherent. Importantly, one study has shown that non-adherence and early-discontinuation were associated with significantly worse mortality (Hershman et al., 2011).

Therapy related side effects are the biggest reason for non-compliance to adjuvant endocrine breast cancer therapy (Guth et al., 2011). The main side effects noted by patients leading to not continuing therapy include arthralgias, hot flashes, gynecological symptoms, and venous thromboembolic events. There are pharmacological and nonpharmacological solutions to these side effects that can alleviate these side effects, such as the use of venlafaxine or gabapentin for hot flashes (Cella and Fallowfield, 2008). Postmenopausal endocrine therapy should be tailored to the individual and the initial selection of tamoxifen or an aromatase inhibitor may be largely due to patient preference to avoid certain side effects.

The possibility of genetic variation to account for side effects has been explored in a genome-wide association (GWAS) study of patients enrolled on the MA.27 trial which randomized patients to five years of anastrazole or five years of exemestane (Ingle et al., 2010). Control patients without any musculoskeletal side effects were compared to patients who reported musculoskeletal side effects. There were four single nucleotide polymorphisms (SNPs) that were observed in patients who developed side effects. These SNPs were clustered on chromosome 14 near the T-cell leukemia1A gene (*TCL1A*). The expression of this gene was shown to be estrogen dependent and was related to interleukin 17 receptor expression. This suggests that the musculoskeletal side effects of AIs in certain patients may be cytokine-mediated. This warrants additional exploration as it would be helpful to identify patients at greater risk of side effects, and potentially offer those individuals non-aromatase inhibitor therapy.

12. Clinical challenges: pharmacogenomics

Pharmacogenomics is the study of individual genetic variations that may influence the efficacy of a drug. Tamoxifen itself is a weak SERM, but tamoxifen is metabolized by the CYP2D6 to its metabolite endoxifen which is much more potent. Variations in tamoxifen metabolism by CYP2D6 may occur via one of two potential mechanisms, either via genotypic variations that result in suboptimal function or via interaction with other drugs that affect CYP2D6 activity (Higgins and Stearns, 2011). The CYP2D6 allele varies greatly by race and ethnicity. In the Caucasian population, about 7% of the population is homozygous for the null allele. In the Asian population, greater than 50% have been found to have reduced activity of the enzyme (Garte et al., 2001).

Some studies have shown that women with reduced activity of the CYP2D6 alleles may have worse breast cancer outcomes than women with two alleles with normal activity or wildtype alleles. Depending on the alleles present, patients can be divided into poor, intermediate, or extensive metabolizers of tamoxifen. The first study to suggest a possible interaction retrospectively assessed women enrolled on a NCCTG trial of adjuvant tamoxifen. Women found to have a genotype consistent with poor metabolism had higher rates of disease recurrence and lower incidence of hot flashes (Goetz et al., 2005). Additional retrospective analyses showed similar detriments in outcome in poor metabolizers (Schroth et al., 2009; Kiyotani et al., 2010). Other large studies, however, have not

demonstrated these effects and currently it is unknown what role variations in CYP2D6 play in tamoxifen resistance (Leyland-Jones et al., 2010; Rae et al., 2010).

CYP2D6 plays a role in the metabolism of many other drugs in addition to tamoxifen. About 25% of common medications including tramadol, codeine, metoprolol and many selective serotonin re-uptake inhibitor (SSRI) antidepressants have been found to affect diminish CYP2D6 metabolism. Sertraline and duloxetine have been found to inhibit CYP2D6 only moderately, whereas paroxetine and fluoxetine have been found to be strong CYP2D6 inhibitors. Some studies have shown that concomitant use of these drugs with tamoxifen can affect the ability of CYP2D6 to synthesize endoxifen from tamoxifen (Ingelman-Sundberg, 2005). Although some advocate testing for CYP2D6 genotypes, at this time there is insufficient data to support doing this (Dieudonné et al., 2009). There have not been any prospective studies to investigate this matter and only retrospective studies are available that are limited in scope (Higgins, 2010) Investigators have found no significant difference in recurrent cancer risk in women taking tamoxifen with a weak CYP2D6 inhibitor citalopram and women taking tamoxifen alone (Ahren et al., 2009). Despite the uncertainties in the available data, it is reasonable to avoid the use of medications that inhibit CYP2D6 in women who are on tamoxifen. However, if a patient is deriving considerable benefit from a drug that inhibits CYP2D6, such as one of the SSRIs, the risk-benefit ratio may weigh in favor of continuing the SSRI.

13. Conclusions

Despite nearly a century of clinical trials, the optimal care for patients with ER+ breast cancer continues to evolve. The optimal ascertainment of target via IHC, enhanced by predictive and prognostic assays and the selection of patients for whom endocrine therapy alone will be curative is the current standard of care for patients with ER+ disease in the adjuvant setting. There are excellent therapies in the form of tamoxifen and estrogen deprivation strategies, which are curative for many patients with early stage disease, and the current challenges involve the selection of the most efficacious, individualized therapies for each patient. As science continues to evolve on a genomic level, it is hoped that the best endocrine therapies will eventually be able to be predicted by toxicity as well as efficacy endpoints.

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