

Hormone Therapy in Breast Cancer: Where do We Stand?

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Abstract

Breast cancer is not only the most common malignancy but also the leading causes of cancer-related deaths in women worldwide. The management of breast cancer is subtype driven and determination of hormone receptor [HR] status, a major driving force for the tumor growth is of paramount importance. The use of hormone therapy [HT] to treat HR positive breast cancer is practiced for more than a century and is one of the pivotal examples of precision medicine.

The present perspective focuses on the state of the art hormone therapy for early and advanced breast cancer in both pre and post-menopausal women. Recent advances in HT strategies, with respect to single or combination therapy use, adding agents targeting HT resistance, checkpoint inhibitors, and optimal duration of endocrine therapy are also being addressed. Opportunities for individualized patient care are discussed.

Keywords: Hormonal therapy; Breast cancer; ER beta

Introduction

Evolution of hormonal therapy

Breast cancer is the commonest malignancy in women. The numbers of new cases of female breast cancer in 2015 were 125.0 per 100,000 women per year. The numbers of deaths were 21.5 per 100,000 women per year [1]. In 1878, Thomas Beatson, from University of Edinburgh, noticed that the breasts of rabbits stopped producing milk after he removed the ovaries. He found that oophorectomy often resulted in improvement for breast cancer patients. He also suspected that "the ovaries may be the exciting cause of carcinoma" of the breast. He had discovered the stimulating effect of the female ovarian hormone (estrogen) on breast cancer, even before the hormone itself was discovered [2]. He also found that there is a similarity between lactating breasts and breast cancers, Estrogen receptors were found to be present in breast cancers way back in 1970 [3]. Prolonged estrogen exposure in the form of early menarche, later menopause, nulliparous state, all of these are associated with increased risk of breast cancer [4-6]. In breast cancer, approximately 80% of all postmenopausal women and 50% of all premenopausal women exhibit Hormone Receptor-Positive (HR+) disease.

Molecular basis of hormonal therapy

Estrogen exerts its effect on breast cancer with primarily 2 types of estrogen receptor subtypes, ER alpha and ER beta. The most widely accepted theory holds that estradiol, acting through Estrogen Receptor Alpha (ERα), stimulates cell proliferation and initiates mutations arising from replicative errors occurring during pre-mitotic DNA synthesis. The promotional effects of estradiol then support the growth of cells harboring mutations [7]. Laboratory and epidemiological data also suggest that non-receptor mediated mechanisms resulting from the genotoxic effects of estrogen metabolites are involved in breast cancer development.

Types of hormonal therapy

The sites of estrogen production are primarily ovaries in premenopausal, and adipose tissue in postmenopausal [8]. The various modalities of hormonal therapies are discussed below:

Blocking ovarian function: This can be achieved by three methods, surgical oophorectomy, radiotherapy induced ovarian ablation and medical oophorectomy.

Surgical oophorectomy (SO): This involves the surgical removal of both the ovaries either via laparoscopy or by small incision surgery. One Randomised Controlled Trial (RCT) compared SO with tamoxifen. Initial treatment responses were seen in ten of 27 patients (37%) treated with oophorectomy and seven of 26 patients (27%) treated with tamoxifen. The difference was not statistically significant [9].

Ovarian irradiation (RO): Treatment algorithms are variable, ranging from 450 cGy in one fraction to 1000-2000 cGy over five to six fractions. Radiation-induced ovarian ablation is a safe and simple outpatient approach. Its disadvantage is that it may be incomplete or reversible in some women. In a meta-analysis of over 3000 patients from six RCT, pooled analysis show a significant amenorrhoea rate and increased Progression Free Survival (PFS) rates. Radiotherapy doses of 1,500 cGy in five fractions, 1,500 cGy in four fractions, 1,600 cGy in four fractions, and 2,000 cGy in ten fractions were associated with excellent amenorrhea rates [10].

Medical ovarian ablation: Potentially reversible castration can be accomplished using Luteinizing Hormone Releasing Hormone (LHRH) agonists, which are also known as Gonadotrophin-Releasing Hormone (GnRH) agonists. LHRH bind to pituitary GnRH receptors with superior affinity and a longer half-life than endogenous LHRH, resulting in internalization of pituitary GnRH receptors and cause the gonadotropic cells refractory to endogenous LHRH. Goserelin is the most studied and commonly used GnRH agonist. The usual dose is 3.6 mg subcutaneous every monthly. Both the German and the Italian study groups have shown that goserelin is effective in metastatic breast

cancer and produces a response rates ranging from 30% to 45% [11,12]. Goserelin was compared to surgery in randomised controlled trial, where there was no difference in the Failure Free Survival (FFS) and Overall Survival (OS) [13]. Another 2 × 2 factorial design RCT compared goserelin with ovarian ablation with or without tamoxifen, and concluded that goserelin is equally effective as ovarian ablation, and the combination of tamoxifen with goserelin was not better than goserelin alone [14].

Blocking estrogen receptors: Aromatase is an important enzyme in the pathway of conversion of androstenedione to estrogen in the peripheral adipose tissue. Aromatase Inhibitors (AI) is a class of drugs that inhibit this enzyme, leading to reduced peripheral conversion of androgen to estrogen. There are 2 classes of AI. Type I steroidal AIs, such as exemestane and formestane are androgen-like compounds that bind permanently to the substrate-complex, resulting irreversible inactivation of the enzyme. Type II non-steroidal AIs, such as aminoglutethimide, letrozole, and anastrozole are nonsteroidal compounds that temporarily bind to the heme-iron component of the aromatase enzyme, thereby prevent the conversion of androgen to estrogen in an indirect manner [15]. Commercially available AIs are: anastrozole (Arimidex), exemestane (Aromasin) and letrozole (Femara) (Table 1).

Generation	Type 1 (steroidal)	Type 2 (nonsteroidal)
First	None	Aminoglutethimide
Second	Formestane	Fadrozole
Third	Exemestane	Anastrozole Letrozole Vorzole

Table 1: Classes of AIs.

Blocking estrogen effects: In the premenopausal women, the major source of estrogen is ovarian tissue. So to have an optimal antiestrogenic effect, the terminal endpoint, i.e., estrogen action, has to be blocked. This can be achieved by two ways:

- **Selective estrogen receptor modulators (SERMs):** Estrogen acts via ER alpha or ER beta receptors. The SERMs are a group of agent that have differential action on different tissue. In some they act as estrogen agonist, in some, as antagonist. The agents used in breast cancer act on breast tissue with antagonistic role, and on tissues like uterus and bone as agonist. The commonly used SERMs are tamoxifen, raloxifene and toremifene (Figure 1) [16].
- **Selective estrogen receptor downregulator (SERDs):** These are agent which largely have antagonistic activities. The need for the development and use of these drugs came from the fact that there are some proestrogenic side effects that may be harmful to the patient. This problem is countered by the use of SERDs. The main mechanism of action is impaired dimerization, augmented estrogen receptor turnover, and disturbed nuclear localization. Fulvestrant is the most studied agent in breast cancer [17]. The standard dose of fulvestrant is 500 mg intramuscularly on days 0, 14 and 28, and then, every 28 days [18].

Miscellaneous: The other hormonal therapies are as follows:

- **Androgens:** Androgen drugs are used to block the ability of the pituitary gland to control estrogen production. They are mostly used for relapsed recurrent and metastatic breast cancer after

failure of most effective therapies. The most common androgen drug used for breast cancer is fluoxymesterone (Halotestin). Fluoxymesterone can cause changes in menstrual periods, male-pattern hair growth, hoarse voice and enlarged clitoris. Bicalutamide has also being shown to have some effect recently is some phase 2 studies and case reports [19,20].

- **Progestins:** Progestins bind to progesterone receptors counteracts certain estrogenic effects and also leads to reduced estrogen production. Some responses with megestrol is seen in breast cancer who have failed with multiple previous therapies [21,22]. Megestrol can cause side effects such as increased appetite, weight gain, rounded face, raised blood pressure, constipation, blood clots, hot flushes and sweats.

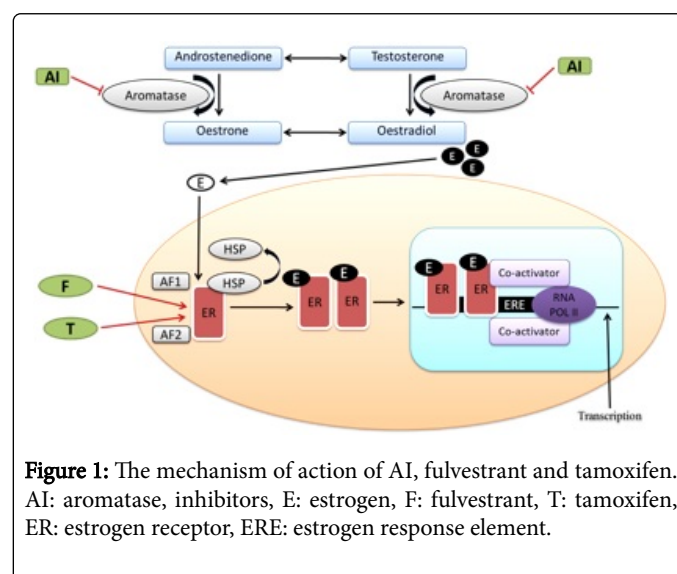


Figure 1: The mechanism of action of AI, fulvestrant and tamoxifen. AI: aromatase, inhibitors, E: estrogen, F: fulvestrant, T: tamoxifen, ER: estrogen receptor, ERE: estrogen response element.

Hormonal Therapy in Breast Cancer

Hormonal therapy slows the growth and spread of breast cancer cells by changing hormone levels in the body, or by stopping breast cancer cells from using estrogen. It is used only in women who have breast cancer and are ER+ and PR+.

Hormonal therapy in breast cancer can be used:

- As an adjuvant HT after surgery and radiation therapy As neo-adjuvant therapy before surgery, to shrink the primary tumor
- As part of a combined treatment approach
- To decrease the chance of cancer developing in the opposite breast
- To treat breast cancer that has recurred
- As a palliative therapy for pain or to control the symptoms

Definition of Menopause

Before we delve into the existing data on the use of these agents, we need to have a clear definition of what is called a menopause. The most widely used definition as proposed by the NCCN guidelines is as follows:

1. Women older than 60 yrs of age
2. Women younger than 60 yrs if:
 - They previously underwent a bilateral oophorectomy.

- They have not had any menstrual periods for 12 months or more in the absence of tamoxifen, chemotherapy, or ovarian suppression, and the serum estradiol is in the postmenopausal range.
- They are amenorrheic on tamoxifen, and follicle-stimulating hormone (FSH) and serum estradiol are in the postmenopausal range.

Early stage breast cancer

Premenopausal: As per latest evidence, the best way to classify premenopausal is to divide them on the basis of presence or absence of risk factors, rather than “one size fits all” strategy.

Presence of high risk features: There is no universally accepted criteria for high risk, but the ones commonly followed in clinical practice are : pathologically involved lymph nodes, large tumor size, high tumor grade, lymphovascular invasion, and/or high risk of recurrence based on a genomic assay (e.g., Recurrence Score (RS) >31 on the 21-gene recurrence assay). In addition, women at a younger age (i.e. age ≤ 35 years) are also at a higher risk of recurrence.

For patients with high risk factors: Studies have shown that the best option for such patient is a combination of Ovarian Ablation (OA) with exemestane, rather than tamoxifen alone [23].

For patients who do not have high risk feature: The best option for them is tamoxifen as single agent. An Aromatase Inhibitor (AI) is not appropriate as single-agent therapy for women with intact ovarian function. This includes premenopausal women who became amenorrheic as a result of adjuvant chemotherapy (i.e. chemotherapy-induced amenorrhea) because they may have return of ovarian function during follow-up or may experience reactivation of ovarian function on an AI.

Tamoxifen alone: Tamoxifen was first approved by FDA for use in advanced breast cancer in 1977. After several years, its approval in adjuvant setting came. In the earliest EBCTCG guidelines published in 1988, treatment with tamoxifen was significantly associated with reduction in the mortality. However, quite surprisingly, in the tamoxifen trials, there was a clear reduction in mortality only among women more than 50 yrs [24]. In the second publication, tamoxifen was associated with significant reduction in mortality, and ovarian ablation was associated with similar effects in less than 50 yrs age [25]. In the most recent analysis, tamoxifen was found to significantly reduce the 15-year risks of breast cancer recurrence and death. ER status was the only recorded factor importantly predictive of the proportional reductions [26].

Duration of tamoxifen: The duration of 5 yrs of tamoxifen comes from the EBCTCG meta-analysis, and it has shown to extent the benefit up to 10 yrs. Although the NASBP B14, Scottish adjuvant tamoxifen studies and a metanalysis did not show any advantage of using tamoxifen for more than 5 yrs [27-29], the other trials supports the use of tamoxifen for more than 5 yrs, extending up to 10 yrs [30,31]. Based on these studies, the ASCO guidelines suggest that if women are pre- or perimenopausal and have received 5 years of adjuvant tamoxifen, they should be offered 10 years total duration of tamoxifen. If women are postmenopausal and have received 5 years of adjuvant tamoxifen, they should be offered the choice of continuing tamoxifen or switching to an aromatase inhibitor for 10 years total adjuvant endocrine therapy [32].

Tamoxifen with ovarian suppression: Initially, single agent tamoxifen was the standard of care for adjuvant hormone therapy in

premenopausal patients. The value of adding ovarian suppression over tamoxifen was unknown. In 2003, the International Breast Cancer Study Group (IBCSG) initiated two randomised, phase 3 trials, the Suppression of Ovarian Function Trial (SOFT) and the Tamoxifen and Exemestane Trial (TEXT), involving premenopausal women with hormone-receptor positive early breast cancer. SOFT was designed to determine the value of adding ovarian suppression to tamoxifen and to determine the role of adjuvant therapy with the aromatase inhibitor exemestane plus ovarian suppression in premenopausal women [23]. In the SOFT trial, patients were randomised to tamoxifen, tamoxifen with ovarian suppression or exemestane with ovarian suppression. The overall population did not show and benefit of adding ovarian suppression. However, in the high risk group, which involves young patients less than 35 yrs, >3 nodes positive, higher tumor grade, combination appears to be beneficial. This benefit in disease free survival comes at the cost of increased post-menopausal symptoms of bone loss and hot flashes. So, the treatment option should be discussed with the patient. In the ABCSG 12 trial, the combination of tamoxifen with goserelin was tested against anastrozole with goserelin. There was no difference between the groups. In fact, in obese patients, had 50% increases in the risk of recurrence [57]. An EBCTCG meta-analysis also showed that there is no advantage of adding OS over tamoxifen in the risk of recurrence [33,34].

Postmenopausal women: The drugs used for these patients are AI or SERMs. Presently AI therapy is a standard of care for the treatment of most postmenopausal women with early-stage breast cancer. Numerous randomized trials of tamoxifen vs. AI as single agent or given in combination or sequentially have been performed with the main motive of comparing DFS and OS in postmenopausal patients with breast cancer. One of the largest hormonal adjuvant trials conducted for postmenopausal patients with early-stage breast cancer is Arimidex®, Tamoxifen, Alone or in Combination (ATAC) trial. The ATAC trial demonstrated long-term superior efficacy and safety of anastrozole over tamoxifen as initial adjuvant therapy for postmenopausal women with HR+ early breast cancer [35]. In the Italian Tamoxifen and Anastrozole Trial by Boccardo et al. investigated the strategy of endocrine therapy crossover from tamoxifen to anastrozole. HR+ breast cancer patients (n=480) who had been receiving tamoxifen (20 mg/day) for 2 or more years were randomly assigned to continue with tamoxifen for as long as a total of 5 years or to switch to anastrozole (1 mg/day) [36]. It showed that switching to anastrozole after the first 2 to 3 years of treatment is well tolerated and significantly improved EFS and RFS in postmenopausal patients with early breast cancer. Similarly, the ABCSG study also showed similar results [37]. Regarding switching to exemestane after tamoxifen, one study proved this approach to be beneficial [38].

When compared to tamoxifen, letrozol, and also exemestane upfront was clearly favoured over tamoxifen [39,40]. The standard duration of AI therapy was 5 yrs, till recently, the updated analysis showed improvement in DFS if letrozole is used for 10 yrs [41]. As of now, there is no evidence suggesting the use of fulvestrant in the early breast cancer setting.

Metastatic breast cancer

Premenopausal

Ovarian ablation: In the initial MA 1 study, OA was shown to be of same efficacy as tamoxifen [42]. In a meta-analysis of individual patient data, there was no difference in overall response rate between tamoxifen and oophorectomy across the four trials (p=0.94, Mantel-

Haenszel test). The odds reduction for progression was $14\% \pm 12\%$ and for mortality $6\% \pm 13\%$ in favour of tamoxifen, results which were not statistically significant ($p=0.32$ and 0.72 , respectively) [43].

Combination of tamoxifen and OA: An Italian study compared goserelin with or without tamoxifen, and there was no difference in the outcomes, and there were more side effects in the combination arm [14]. In another controlled study, buserelin with tamoxifen was better than buserelin or tamoxifen alone with improved survival [44]. However, in a meta-analysis, with a median follow-up of 6.8 years, there was a significant survival benefit (stratified log-rank test, $P=0.02$; hazards ratio [HR]=0.78) and progression-free survival benefit (stratified log-rank test, $P=0.0003$; HR=0.70) in favour of the combined treatment. The overall response rate was significantly higher on combined endocrine treatment (stratified Mantel Haenszel test, $P=0.03$; odds ratio=0.67) [45].

Tamoxifen: After a meta-analysis of few small trials, that demonstrated the comparability of tamoxifen to the historical standard of ovarian ablation and then tamoxifen was extensively adopted as first-line therapy for premenopausal women with HR+ MBC because of its convenience, safety, and tolerability [43]. It is the most commonly employed first line regimen for premenopausal women.

Tamoxifen versus OS: Few randomized studies compared OA with tamoxifen therapy for premenopausal women. One of them was a meta-analysis. In these trials tamoxifen and OA generally seemed to show equivalent outcomes [9,43,46].

Postmenopausal

Aromatase inhibitors: According to a cochrane meta-analysis, the use of AI in postmenopausal is justified compared to other hormonal therapies. Thirty-seven trials were identified, 31 of which were included in the main analysis of any AI versus any other treatment (11,403 women). The pooled estimate showed a significant survival benefit for treatment with an AI over other endocrine therapies (HR 0.90, 95% CI 0.84 to 0.97). A subgroup analysis of the three commonly prescribed AIs (anastrozole, exemestane, letrozole) also showed a similar survival benefit (HR 0.88, 95% CI 0.80 to 0.96). There were very limited data to compare one AI with a different AI, but these suggested an advantage for letrozole over anastrozole [47]. In another meta-analysis, letrozole seemed to be significantly better than tamoxifen in terms of time-to-progression (TTP) (HR=0.70 (95% CI: 0.60, 0.82)), objective response rate (RR=0.65 (95% CI: 0.52, 0.82)) and quality-adjusted time without symptoms or toxicity (Q-Twist difference=1.5; $P<0.001$). Exemestane seemed significantly superior to tamoxifen in terms of objective response rate (RR=0.68 (95% CI: 0.53, 0.89)). Anastrozole seemed significantly superior to tamoxifen in terms of TTP in one trial (HR=1.42 (95% CI: 1.15, NR)), but not in the other (HR=1.01 (95% CI: 0.87, NR)). In terms of adverse events, no significant differences were found between letrozole and tamoxifen [48].

Fulvestrant: Fulvestrant is an estrogen receptor antagonist that blocks ER dimerization and DNA binding, increases ER turnover, and inhibits nuclear uptake of the receptor. Because it blocks ER function before estrogen can bind the receptor, fulvestrant can theoretically overcome resistance that is driven by the agonist properties of tamoxifen. Fulvestrant was compared with tamoxifen in a randomised trial, where the dose of fulvestrant was 250 mg once monthly. At a median follow-up of 14.5 months, there was no significant difference between fulvestrant and tamoxifen for the primary end point of time to progression (TTP; median TTP, 6.8 months and 8.3 months,

respectively; hazard ratio, 1.18; 95% CI, 0.98 to 1.44; $P=0.088$) [49]. Fulvestrant was compared with anastrozole, where the dose was 250 mg monthly. The median survival was similar in both the arms. However, later it was realised that probably the actual dose of fulvestrant that is effective is 500 mg and not 250 mg. This was proven in the confirm trial, where fulvestrant 500 mg is associated with a 19% reduction in risk of death and a 4.1-month difference in median OS compared with fulvestrant 250 mg. Fulvestrant 500 mg was well tolerated, and no new safety concerns were identified [18,50]. Fulvestrant was also shown to be beneficial compared to anastrozole other phase III randomised trials [51]. In the FALCON trial, presented in abstract form till date, 462 patients were randomised to fulvestrant versus anastrozole. Median PFS, which was the primary endpoint, was 16.6 months compared to 13.8 months with anastrozole. Health related quality of life was similar in both the groups. The survival data was 31% mature with the available follow up (ESMO 2016, Ellis et al.).

CDK4/6 inhibitors: CDK 4/6 has been implicated as important mediators of cell signalling, especially in hormone receptor positive breast cancer. Many CDK inhibitors have been tested; with the clinically useful ones are abemaciclib, ribociclib and palbociclib. In a phase II single arm MONARCH study, the confirmed ORR (per RECIST v1.1) was 17.4%, the clinical benefit rate (CR+PR+SD ≥ 6 mos) was 42.4%, and median PFS was 5.7 mos [52]. In the recently published MONALESSA trial with ribociclib, after 18 months, the progression-free survival rate was 63.0% (95% confidence interval (CI), 54.6 to 70.3) in the ribociclib group and 42.2% (95% CI, 34.8 to 49.5) in the placebo group. In patients with measurable disease at baseline, the overall response rate was 52.7% and 37.1%, respectively ($P<0.001$) [53]. The first of the CDK inhibitors to be approved was palbociclib. In a phase III trial of patients who progressed after prior hormone therapy, the median progression-free survival was 9.2 months (95% confidence interval [CI], 7.5 to not estimable) with palbociclib-fulvestrant and 3.8 months (95% CI, 3.5 to 5.5) with placebo - fulvestrant (hazard ratio for disease progression or death, 0.42; 95% CI, 0.32 to 0.56; $P<0.001$) [54]. Also in first line, palbociclib has been tested in a phase III trial along with letrozole (PALOMA II), where the median PFS was 24.8 months in combinations arm vs. 14.5 months in letrozole with placebo (HR=0.58 (0.46-0.72), $P<0.000001$). ORR was improved with combination (42.1% vs. 34.7%, $P=0.031$; 55.3% vs. 44.4% in patients with measurable disease ($P=0.013$)). CBR was 84.9% vs. 70.3% ($P<0.0001$) [55].

PI3K inhibitors: Buparlisib, which is a pan PI3K inhibitor, was tested in a phase III randomised trial, in combination with fulvestrant in hormone refractory breast cancers, which was presented in abstract form [56,57]. In this study, the patients who received fulvestrant alone had a progression-free survival of 5 months; those who received buparlisib plus fulvestrant had a progression-free survival of 6.9 months (hazard ratio [HR]=0.78; $P<0.001$). Patients who had mutant PIK3CA detected in their circulating tumor DNA had much better outcomes if they received buparlisib plus fulvestrant compared with those who received fulvestrant alone: progression-free survival of 7 months in the buparlisib-plus-fulvestrant group vs. 3.2 months in the fulvestrant-alone group (HR=0.56; $P<0.001$).

Conclusion

The journey of hormonal therapy in breast cancer has been a long one, starting from single agent to combinations, also testing the timing of various therapies. However, even with the best possible treatment, many patients die of progressive disease. There is extensive research

going on in the field of alternate pathways that are involved in the development of resistance. With every coming day, new insights are being made with the advent of newer targeted agent. We are sure to delve into a bright future in the field of hormone positive breast cancer.

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