Review Article

Endocrine Therapy for Breast Cancer - A Success Story in All Treatment Settings

Kumar S*, Burney IA, Al-Moundhri MS
Sultan Qaboos University Hospital, Muscat, Oman

*Corresponding author: Kumar S, Sultan Qaboos University Hospital, Muscat, Oman; Email: bhagia1@ yahoo.com

Abstract

Endocrine treatment for hormone receptor positive breast cancer has a proven role in all settings, ie neo-adjuvant, adjuvant and palliative care. Tamoxifen had been the standard of care for all women with breast cancer in adjuvant setting for many years by improving the disease free survival (DFS) and overall survival (OS). Tamoxifen remains the only approved treatment in all settings for pre-and peri-menopausal women with breast cancer. Aromatase inhibitors (AIs) later became the standard of care in all treatment settings for post-menopausal women by demonstrating advantage in DFS and in some studies OS. Ovarian function suppression (OFS) was tested in many trials and proved to be effective in adjuvant and metastatic settings but was never used routinely. Recently, 2 large trials also showed advantage with the addition of OFS to AIs as compared to OFS and tamoxifen in pre-menopausal women. Fulvestrant is another option for women with stage IV breast cancer. More recently, modulation of endocrine resistance with mammalian target of rapamycin (mTOR) inhibitor has been reported in patients with metastatic breast cancer and is being tested in other settings. This review summarizes the major advances in endocrine treatment of receptor positive breast cancer in all settings.

Keywords: Breast Cancer; Estrogen receptor; Progesterone receptor; Tamoxifen; Anastrazole; Letrozole; Exemestane; Fulvestrant

Introduction

Breast cancer remains the most common cancer in women world over. Overall, it is the second most common cancer after lung cancer. In 2012, 1.67 million new cases of breast cancer were diagnosed and 522,000 deaths were recorded [1]. Although the incidence is higher in the developed countries, numerically more patients are diagnosed to have breast cancer in middle and low income countries, and is most common cause of cancer related mortality in these countries [1]. Disparities in age, stage and survival between the developed and developing countries have been described in the literature explicitly. Women in developing countries get the diagnosis at a younger age, and more often with advanced stage at presentation [2-4]. The increasing diagnosis at a younger age in developing countries may be secondary to screening programs and to lifestyle factors [5]. It is well known that younger women have less chances of being hormonal responsive (HR) as compared to post-menopausal women (PMW) [2]. A lack of hormone responsiveness not only suggests the presence of more aggressive disease, but also affects the choice of treatment modalities in this patient population.

Current data suggest that around 40-50% of patients in the pre-menopausal phase and upto 50-70% of patients in post-menopausal phase have hormone receptor positive (HRP) disease [6,7]. Estrogen has a key role in cell cycle proliferation in mammary cells. Hence blocking the estrogen receptor (ER) or reducing the peripheral estrogen level has beneficial effect on tumor control [8-10]. Various agents are available to treat patients with HRP (Estrogen receptor (ER) positive and progesterone receptor (PgR) positive) breast cancer. These include tamoxifen, anastrazole, letrozole, exemestane, Fulvestrant, and Goserilin. The choice of a particular agent depends on many factors including patient's age, menopausal status, treatment setting, potential side effects, availability, and patient preferences.

In rest of the article, evidence regarding the choice of particular endocrine agent will be discussed for different treatment settings followed by upcoming strategies in overcoming the resistance and improving the outcomes in HRP breast cancer.

Endocrine therapy in neo-adjuvant setting

Neo-adjuvant (NA) systemic therapy results in reducing the tumor size and down staging and hence results in organ preservation and also provide in-vivo insight for tumor response to particular treatment [11,12]. NA chemotherapy (NACT) is considered standard of care in breast cancer [13].

In a phase II trial NACT was compared with NA hormonal therapy (NAHT) in 95 women with HRP breast cancer. PMW received exemestane as single agent while pre-menopausal patients received exemestane with goserelin. Response rates (RR) were better with NACT as compared to NAHT (66% vs. 48%, p = 0.075). However, there was no difference in breast conservation surgery (BCS) rates [14].

In another large phase II trial, 239 PMW with HRP, stages II – IIIB breast cancer were randomized to receive NAHT (exemestane or anastrazole) or NACT (doxorubicin and paclitaxel x 4 cycles). There was no difference in primary endpoint of objective RR in both arms and in the secondary endpoint of BCS. Response was assessed clinically as well with mammogram and ultrasonography [15].

Generali D et al. randomized 114 PMW with HRP breast cancer

to letrozole and letrozole plus metronomic cyclophosphamide. After 6 months, overall RR was better in the combination arm as compared to the single agent letrozole (87.7% vs. 73.2%). However, there was no difference in terms of complete response (CR, 43.8% vs. 41.1%) [16].

In a phase III, multicenter trial, PMW with HRP breast cancer were randomized to anastrazole or tamoxifen. Chemotherapy was also permitted. Among patients who were only treated with endocrine therapy, responses after 3 months of therapy were better for anastrazole (p = 0.07). Higher benefit in terms of operability was also seen in the anastrazole arm [12].

In a large double blind phase III randomized trial, 4 months of letrozole was reported to be superior to tamoxifen in NA setting for PMW with HRP breast cancer. Patients in the letrozole arm had superior clinical (p = <0.001) and radiological responses (p = 0.042) with more patients receiving BCS in the letrozole arm (p = 0.022) [17].

Study of Tamoxifen or Arimidex, combined with Goserelin acetate, to compare Efficacy and safety (STAGE) trial randomized 197 pre-menopausal women with ER positive and Her2 negative breast cancer to 6 months of NAHT. Patients in anastrazole with goserelin achieved better tumor regression as compared to tamoxifen with goserelin, clinically (p = 0.004) and radiologically (p = 0.027 for ultrasound and p = 0.0002 for MRI or CT). Patients in the anastrazole and goserelin arm obtained better pathological responses [18].

Immediate Preoperative Anastrozole Tamoxifen or combined with Tamoxifen (IMPACT) trial enrolled more than 300 PMW with HRP breast cancer. After 3 months of treatment no difference was seen in clinical response (24%, 20% and 28% respectively for anastrazole, tamoxifen and the combination arm) or BCS rates (44%, 31% and 24% respectively for anastrazole, tamoxifen and combination arm, statistically insignificant) [19].

Z1031, a randomized, phase II, 3 arm trials by American College of Surgeons Oncology Group, assessed all three AIs in NA setting in HRP, Her2 negative, stage II-III breast cancer in PMW. More than 100 women in each arm were treated for 16-18 weeks. Clinical RR was not significantly better in any arm (62.9%, 74.8% and 69.1% for exemestane, letrozole and anastrazole respectively). BCS rates were not different among all three arms either [20].

Different studies have used variable treatment duration in NA setting before surgical intervention hence optimal duration of NA hormonal treatment is not completely defined. It is obvious from the results of different studies that longer treatment duration with endocrine therapy increases the RR and BCS. In a small phase IIb/III German trial response rate with 4 months of NA letrozole was 62.5% which increased to 70% with more treatment duration which also translated in more BCS [21].

In a British study, 182 PMW with HRP breast cancer were treated with NA letrozole. After 3 months of treatment most of those patients responded; but 63 were still deemed inoperable though responding. Those 63 women were treated for more than 3 months and 23 patients continued treatment for more than 2 years. Investigators assessed continuous reduction of tumor size in all those patients (median reduction in size of 50% between 3-6 months and 33% at12-24 months) [22].

Taken together, the studies on the use of NAHT suggests that NAHT could be used as an alternative to NACT in selected patients, the RR and BCS rates are higher with AIs compared to tamoxifen, combination of two hormonal agents do not improve the RR, and both RR and BCS rates improve with longer duration of NAHT.

Endocrine therapy in adjuvant setting

Administration of hormonal therapy to patients with HRP breast cancer in adjuvant setting has been shown to reduce the chance of recurrence and improve the DFS and OS. This effect is independent of chemotherapy administration [23]. Tamoxifen has remained the main treatment option in adjuvant setting for pre and peri menopausal women [10,23-28]. AIs are widely offered to PMW with HRP breast cancer [24]. Other options for hormonal treatment in adjuvant setting are ovarian ablation alone or in combination with tamoxifen or AI [5,25,26]. Each treatment option has its own merits and disadvantages which will be discussed in this section. The duration of treatment and 'switch' methodology will also be discussed.

Tamoxifen

Perhaps the first randomized trial demonstrating survival advantage for tamoxifen in the adjuvant setting was the Nolvadex Adjuvant Trial Organisation (NATO) study. In a follow-up report of the NATO study, investigators reported a gain of 36% in recurrence free survival (RFS) and 29% in OS after 2 years of tamoxifen at median follow-up of 66 months. In this trial premenopausal and PMW with node negative and positive disease were randomized to have no adjuvant treatment vs. adjuvant tamoxifen [29].

In National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 trial, 2644 women (pre and PMW) with node negative, HRP breast cancer were randomized to receive tamoxifen or placebo. There was significant gain in RFS for tamoxifen group (88% vs. 77% with p = <0.00001). Beneficial effect was seen for women in all age groups (>49 or<49 years). There was no OS advantage (p = 0.3) [30]. Of all enrolled patients in this trial, 1172 women who completed 5 years of tamoxifen were re-randomized to continuous tamoxifen or placebo. At a median follow up of 7 years, detrimental outcome was observed for continuous tamoxifen arm. This trial formed the basis for the use of tamoxifen for 5 years in the adjuvant setting for several years [31].

In the Scottish trial of adjuvant tamoxifen, 1323 women (pre and PMW) with HRP breast cancer were randomized to receive upfront adjuvant tamoxifen for 5 years or to start tamoxifen at the time of relapse. Women in the upfront arm achieved significant benefit in terms of DFS (p = 0.007), OS (p = 0.006) and death secondary to breast cancer (p = 0.002). This effect was maintained until 15 years of follow up [32]. After 5 years of tamoxifen, 342 women were consented for re-randomization to continuation of tamoxifen until relapse (n = 173) or to stop treatment (n = 169). There was no difference for DFS or OS for prolonged tamoxifen arm; rather more women experienced endometrial cancer in the extension arm [32,33].

Kaufmann et al. reported results of 2 trials in which tamoxifen at dose of 30mg daily was administered for 2 years. In the first trial, 276 patients with low risk disease were randomized to tamoxifen or chemotherapy (6 cycles of 4 weekly intravenous (IV) cyclophosphamide, methotrexate and 5-fluorouracil [CMF]). Patients in chemotherapy arm had better DFS and OS especially who were

< 49 years of age. Chemotherapy (8 cycles of 3 weekly doxorubicin and cyclophosphamide [AC]) or same chemotherapy together with tamoxifen was compared in 471 women with ER positive high risk disease. There was no difference between the two arms for DFS or OS [34].

In an Italian trial, 504 pre and PMW with stage II, HRP breast cancer were randomized to tamoxifen for 5 years, chemotherapy (CMF 6 cycles, 3 weekly followed by 4 cycles of epirubicin 3 weekly) and same chemotherapy with tamoxifen. Patients in tamoxifen alone and tamoxifen with chemotherapy did better as compared to the chemotherapy only arm. There was no significant difference between tamoxifen and chemotherapy plus tamoxifen arm. Earlier results showed similar efficacy for both pre and PMW, but later follow up revealed that PMW had better outcome with tamoxifen [35,36].

In a large intergroup trial (INT-0102) women with node negative disease were randomized to receive 2 different chemotherapy regimens alone or same chemotherapy followed by 5 years of tamoxifen. Patients with HRP disease had substantial benefit for DFS (p = 0.003) and OS (p = 0.03) with tamoxifen. Patients with HR negative disease showed no benefit with the use of tamoxifen [37].

In another large intergroup trial (E5188), premenopausal women with node positive, HRP breast cancer were randomized to receive anthracycline based chemotherapy alone, same chemotherapy with goserelin and both with tamoxifen. Chemotherapy alone arm was inferior to chemotherapy, goserelin and tamoxifen arm (better DFS with combination of all three) with no OS benefit. Chemotherapy along with LHRH was not superior to chemotherapy alone [38].

A Canadian trial assessed the role of adjuvant tamoxifen for 5 years in early breast cancer patients. Women with HRP as well as negative breast cancer were randomized to tamoxifen and placebo arm. After median follow up of 9.7 years improved DFS was seen for tamoxifen treated patients (hazard ratio (HR), 0.77, p = 0.056) with trend for OS benefit (HR, 0.78, p = 0.12). The study was closed earlier due to slow accrual and could not meet the primary end point of OS [39].

The International Breast Cancer Study Group Trial 13-93 randomized premenopausal node positive women to adjuvant chemotherapy followed by tamoxifen or placebo. Women with ER positive and negative were enrolled on the trial. All patients with ER positive disease achieved a significantly better DFS (HR, 0.59, p = 0.0001). Beneficial effect with tamoxifen was observed for both younger and older (> 40 years) patients [40].

In European Organisation for Research and Treatment of Cancer (EORTC) study 10901, women with stage I to IIIA breast cancer (HRP and negative) were randomized to 3 years of tamoxifen or no treatment after completion of 6 cycles of adjuvant chemotherapy (different regimens). Women on tamoxifen arm had better RFS as compared to control arm (73% vs. 67%, p = 0.035) with no significant difference in OS. Patients with lymph node and ER positive disease benefited with tamoxifen (p = 0.044 and p = 0.014 respectively) [41].

A long-term follow up of the meta-analysis by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) reported efficacy of tamoxifen in adjuvant setting with long lasting effect of more than

10 years for RFS and OS [23,42]. The efficacy of tamoxifen was more prominent in first 4 year for DFS (50%) which reduced to 33% in year 5-9 with very little effect after 10 years of treatment with average risk reduction of 39% over all time periods (risk reduction (RR) of 0.61) [23]. This beneficial effect was not dependent on quantitative ER analysis except for very minimum effect for ER expression of <10 fmol/mg. Tamoxifen reduced the risk of recurrence for patients with node negative (RR, 0.57) as well as node positive (RR, 0.63) disease with 10 year gain of 15.6% (SE 1.4) and 15.5% (SE 3.6) for node negative and node positive disease respectively. Tumor size, tumor grade, patient age and chemotherapy did not affect this beneficial outcome. Tamoxifen also reduced the breast cancer related mortality significantly (RR, 0.7) at 15 years with 15 year gain of 9.2% (SE 1.0) [23].

Tamoxifen has carryover effect beyond 5 years of treatment which persists until 15 years [23,43]. Previous studies for long term tamoxifen (beyond 5 years) showed detrimental effect with prolonged therapy [31,33], but others have criticized those conclusions due to small number of patients who continued on prolonged tamoxifen and consider those adverse findings as play of chance. Hence they suggested large trials to investigate benefit of prolonged tamoxifen therapy [43].

Adjuvant Tamoxifen Longer against Shorter (ATLAS) trial is a large, multinational, randomized study which enrolled more than 12000 patients with breast cancer to 5 or 10 years of tamoxifen. Final analysis was for patients with HRP patients only to assess the benefits RFS and breast cancer related mortality. More than 3000 women with HRP disease were allocated to each arm. With good treatment compliance and follow up, investigators presented the results after 15 years of follow up. Continued treatment of tamoxifen for 10 years reduced the risk of recurrence (absolute RR of 3.7%, HR, 0.84, p = 0.002) and breast cancer mortality (absolute RR of 2.8%, p = 0.01) and overall mortality (p = 0.01) as compared to women who took tamoxifen for 5 years. Patients on longer tamoxifen arm experienced more side effects like endometrial cancer, pulmonary embolism and stroke [43].

The UK adjuvant Tamoxifen— To offer more? (aTTom) trial randomized more than 6000 women to 5 years or 10 years of tamoxifen like ATLAS study. Women on longer duration of treatment benefited with fewer recurrence. The effect was time dependent (RR of 0.99 at 5-6 years and 0.75 after 9 years), less breast cancer related death (p = 0.05) and marginally improved OS (RR = 0.94). Women who were on longer treatment duration had a higher risk of developing endometrial cancer and associated mortality [44].

As a result of the last two trials, different groups are now considering the option of 10 years of tamoxifen for pre and peri-menopausal women with ER positive breast cancer in adjuvant setting [13,24,27,42]. However, the current standard of care remains 5 years of adjuvant tamoxifen in pre- and peri-menopsuasal patients with HRP breast cancer.

Aromatase inhibitors

Role of AIs in adjuvant setting was assessed in several randomized phase III trials for PMW with HRP breast cancer. AIs have been studied as either sole adjuvant treatment, or as sequential therapy

(before or after tamoxifen), or as extended regimen after 4.5 to 6 years of tamoxifen [24,27,28].

More than 5000 PMW with HRP disease were randomized to receive 5 years of tamoxifen or anastrazole in the ATAC study. After 100 months of follow up anastrazole was found to be superior to tamoxifen for DFS benefit (HR, 0.85, p = 0.003 and absolute RR of 2.8% and 4.8% at the end of 5 and 9 years respectively). There was no difference for OS (p=0.7) or death after recurrence (p=0.2). Major side effect with anastrazole was bone fracture while there was no difference in quality of life between the two treatment arms [45].

The Breast International Group (BIG) 1-98 study randomized more than 8000 PMW with HRP breast cancer to 4 treatment arms. Tamoxifen alone, letrozole alone, tamoxifen followed by letrozole and letrozole followed by tamoxifen. After a median follow up of nearly 2 years, results were released for tamoxifen and letrozole arms. DFS advantage at 5 years (HR, 0.81, p=0.003) and distant DFS (HR, 0.73, p=0.001) for women on letrozole was better than tamoxifen. There was no advantage for OS to any treatment arm. More cardiac events were noted in letrozole group while incidence of vaginal bleeding, thromboembolism and endometrial cancer were seen more frequently in the tamoxifen arm [46].

In a large Canadian study more than 7500 PMW with HRP breast cancer were randomized to anastrazole or exemestane for 5 years. After 4 years of median follow up almost similar event free survival was documented for both arms (9.1% vs. 9.2%) with a HR of 1.02 (p=0.85). there was no difference for OS. Liver function derangement, acne, masculinization and atrial fibrillation were more common in exemestane arm while hypertriglyceridemia, hypercholesterolemia and bone loss was more in anastrazole arm. A total of 31.6% of study participants discontinued their treatment at some point due to various reasons [47].

BIG 1-98 study published the results of sequential arms after 71 months of median follow up. There was no difference in DFS or OS for women treated with sequential therapy with 2 years of letrozole followed by 3 years of tamoxifen or 2 years of tamoxifen followed by 3 years of letrozole or letrozole alone. More early relapses were documented in the tamoxifen followed by letrozole arm [48].

The Intergroup Exemestane Study (IES) randomized more than 5000 PMW with HRP disease to 5 years of tamoxifen or switching to exemestane after 2-3 years of tamoxifen in the adjuvant setting. After a median follow up of 2.5 years, more events were noticed in the tamoxifen arm compared to the switch arm. DFS was better for switch therapy (HR, 0.68, p=<0.001) with an absolute benefit of 4.7%. There was no difference for OS (p=0.37) [49]. After 55.7 months of median survival, persistent benefit for DFS was documented for the switch arm (unadjusted HR, 0.76, p=0.0001) with an absolute benefit of 3.3%. Modest advantage for OS was also seen after long-term follow up (HR, 0.83, p=0.05) [50].

Two prospective trials of similar design (the Austrian Breast and Colorectal Cancer Study Group (ABCSG) trial 8/Arimidex-Nolvadex (ARNO) 95) published combined results for PMW with HRP breast cancers, who were assigned to continuous tamoxifen for 5 years or 2 years of tamoxifen followed by 3 years of anastrazole. After 28 months of median follow up, 40% less events were documented in

the switch arm (p=0.0009) with an absolute benefit of 3.1% at 3 years. Fewer events of distant recurrence were observed in the switch arm (HR, 0.61, p=0.0067). More fractures were seen in the anastrazole arm [51]. Kaufmann M et al. reported the follow up results of ARNO 95 study and showed continuous benefit for DFS (HR 0.66, p=0.049) and improved OS (HR, 0.53, p=0.045) [52].

Italian tamoxifen anastrozole (ITA) trial assigned 448 PMW with HRP and node positive breast cancer to tamoxifen and tamoxifen for 2-3 years followed by anastrozole to complete 5 years of adjuvant treatment. Women on the switch arm had fewer events (HR, 0.57, p=0.005) and better DFS (HR, 0.56, p=0.01) with no OS advantage for any treatment arm [53].

Likewise extended duration of hormonal treatment in adjuvant setting with tamoxifen, AIs were tested for additional duration after 5 years of tamoxifen with the hypotheses of reducing the recurrence after stopping tamoxifen, and hence to improve the OS. National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) sponsored MA. 17 trials which accrued more than 5000 PMW with HRP breast cancer to 5 years of letrozole or placebo after 5 years of tamoxifen. Study was stopped a year earlier due to favorable results for letrozole arm at interim analysis. After 2.5 years of median follow up, 4 year DFS was 94.4% for letrozole group and 89.8% for women on placebo arm, with a 4.6% absolute RR favoring letrozole. No OS benefit was seen for overall study population, but the sub group analysis revealed improved OS for women treated with letrozole and had node positive disease at diagnosis (HR, 0.61, p=0.04) [54].

Anastrazole for 3 years or nothing after 5 years of tamoxifen was assessed in ABCSG Trial 6a for HRP, PMW. After more than 5 years of follow up, less recurrences were documented in the anastrazole arm (HR, 0.62, p=0.031) [55].

NSABP B-33 trial was closed prematurely after accrual of 1598 of 3000 planned patients due to the early release of MA 17 trials. The trial was started to assess the efficacy of 5 years of exemestane after 5 years of tamoxifen in adjuvant setting for endocrine sensitive breast cancer in PMW. All 344 patients on placebo arm were allowed to take exemestane. After 30 months of median follow up, intention to treat analysis (ITT) revealed 32% reduction in DFS with an absolute difference of 2% at 4 years (p=0.07) [55].

Taken together, the current standard of care for PMW with HRP breast cancer is either a single agent AI, or switch therapy completing 5 years of hormone therapy. Alternatively, AIs could be used for 5 years after 2-3 years of tamoxifen.

Ovarian ablation or function suppression

Ovarian ablation or OFS improved the DFS (4.3% absolute gain at 15 years; p = <0.001) and OS (3.2% absolute gain at 15 years; p = 0.004) for pre-menopausal women with breast cancer [42]. OFS was tested in many trials as the sole method of treatment and was compared with the chemotherapy. OFS has proved to be effective in improving the DFS and OS with a lesser impact when used after chemotherapy. An explanation is that chemotherapy itself induces OFS [56].

Recently results of 2 large randomized trials were published comparing the efficacy of OFS with tamoxifen and exemestane in

adjuvant setting for HRP premenopausal breast cancer patients. More than 6000 premenopausal patients were enrolled in two randomized, phase 3 trials, the Tamoxifen and Exemestane Trial (TEXT) and the Suppression of Ovarian Function Trial (SOFT) by the International Breast Cancer Study Group (IBCSG). Patients were randomized to gonadotropin releasing hormone agonist triptorelin with tamoxifen or exemestane or tamoxifen alone in 1:1:1 fashion, with DFS as the primary end point. After 68 months of median survival, women in exemestane and OFS arm had better 5 year DFS as compared to tamoxifen and OFS (HR, 0.72, p = <0.001) with no difference in OS (25). SOFT results revealed no significant difference for 5 year DFS for tamoxifen with OFS as compared to tamoxifen alone (HR, 0.83, p = 0.10) but the group of women who continued to remain premenopausal after chemotherapy with high risk disease features benefited with tamoxifen and OFS with an absolute improvement of 4.5% [57].

Endocrine therapy in metastatic setting

Many early trials compared tamoxifen with high dose estrogens, megestrol acetate and diethylstilbestrol for treating metastatic breast cancer (MBC). Tamoxifen was found to be equally effective to megestrol acetate and diethylstilbestrol in earlier small scale trials [55,58,59]. Tamoxifen was also found to be equally effective in comparison with other estrogen receptor modulators like toremifene or idoxifene, but showed better efficacy when compared with droloxifene and arzoxifen [60,61]. In a meta-analysis tamoxifen showed comparable responses to different types of previously used hormonal agents for breast cancer [62].

Anastrazole was tested against tamoxifen as a first line treatment for MBC in 2 randomized trials. In the North American trial, anastrazole proved to be superior to tamoxifen for time to progression (TTP, p = 0.005), however, this result could not be replicated in the Tamoxifen or Arimidex Randomized Group Efficacy and Tolerability (TARGET) study. The difference in results could be explained by the difference in patient population, as 90% of patients in the North American study had HRP disease while only 45% patients in the TARGET study had endocrine sensitive disease. Analysis for patients with HRP disease showed beneficial effect of anastrazole for TTP (10.7 vs. 6.4 months; p = 0.022) [63]. The first, as well as updated results of both the studies also did not reveal any survival benefit [64].

Letrozole was compared against tamoxifen for MBC in PMW with HRP or unknown status. Letrozole treated patients showed better overall objective responses (32% vs. 21%, p = 0.0002), longer TTP (9.4 vs. 6.0 months p = <0.0001) and treatment failure but no difference in OS [65].

In another phase III trial, PMW with endocrine sensitive MBC were allocated to exemestane or tamoxifen. Patients on exemestane had better responses as compared to tamoxifen (46% vs. 31%, p = 0.005) but no difference in DFS or OS was seen [66].

Fulvestrant was tested at previously approved dose of 250mg monthly against tamoxifen and anastrazole and proved to be non-inferior against both the agents [67,68]. In the Evaluation of Faslodex versus Exemestane Clinical Trial (EFECT), postmenopausal women with endocrine sensitive MBC with progressive disease on previous hormonal treatment were randomized to exemestane or loading dose fulvestrant regimen (500mg day 0 and 250mg on day 14, 28 and then monthly). Both the treatment showed similar responses, duration of response and TTP [69].

The Study of Faslodex with or without concomitant Arimidex or Exemestane following progression on non-steroidal Aromatase inhibitors (SoFEA) randomized PMW with HRP breast cancer to loading dose fulvestrant with or without exemestane or exemestane alone. There was no benefit of addition of fulvestrant to exemestane for DFS (HR, 1.0, p = 0.98) and responses were comparable with single agent exemestane (HR, 0.95, p = 0.56). No significant difference for OS was noticed for all 3 arms [70].

High dose fulvestrant (500mg on day 0, 14 and 28 followed by 4 weekly) was tested against 250mg 4 weekly in Comparison of Faslodex in Recurrent or Metastatic Breast Cancer (CONFIRM) trial. No significant difference was seen for response rates but TTP was noticed for high dose arm (6.5 vs. 5.5 months, HR, 0.8, p = 0.006) with a trend toward survival benefit (HR, 0.84, p = 0.091) as well [71].

A phase II trial FIRST (Fulvestrant First-Line Study Comparing Endocrine Treatments) assessed high dose fulvestrant with anastrazole as first line treatment in MBC and found no difference in response rates, but longer TTP (not reached vs. 12.5 month, HR, 0.63, p = 0.049) [72]. Follow up study of this trial showed persistent benefit for fulvestrant arm for TTP (23.4 vs. 13.1 months, HR, 0.66, p = 0.01) [73].

In Fulvestrant and Anastrozole Combination Therapy (FACT) study, previously treated patients were randomized to loading dose fulvestrant plus exemestane or exemestane alone. No difference for disease response, TTP or OS was documented between the two arms [74]. In another phase III trial similar regimen was tested in PMW with MBC as first line. Improvement for DFS (15.0 vs. 13.5 months, HR, 0.80, p = 0.007) and OS (47.7 vs. 41.3 months, HR, 0.81, p = 0.049) favored combination arm. Unplanned analysis showed better responses for patients who were naïve to hormonal treatment [75].

Overall, the use of AIs has led to improvement in RR, DFS, and sometimes in OS in patients with MBC, and is now the standard of care. However, addition of fulvestrant to AIs has met with equivocal results, and is not currently recommended.

Resistance to endocrine therapy

Resistance to cancer treatment has been a major concern among treating physicians and scientists. All cancers develop resistance to drugs during the treatment course (acquired resistance) while some cancer have resistance to treatment modalities at the start (de novo resistance). Two large meta-analyses have proved that nearly 1/3 of patients treated with tamoxifen and 17% treated with AIs developed disease recurrence [76-78]. Multiple mechanisms are responsible for acquired resistance to endocrine treatment for breast cancer. These include epidermal growth factor receptor (EGFR) and HER2, phosphatidylinositol 3-kinase (PI3K) and mitogen-activated protein kinase (MAPK/ERK) and fibroblast growth factor receptor 1 (FGFR-1) [16,76,77]. Preclinical studies have shown significant role of PI3K and its downstream effector the mammalian target of rapamycin (mTOR) in endocrine resistance [76,77]. Besides this another study found association of treatment response with increased levels of pER-α and decreased p44/42 MAPK and treatment resistance with increased p44/42 MAPK and HIF-1α [16].

Various studies have investigated the addition of mTOR inhibitors along with anti-estrogens to overcome the resistance and improve the disease response. Many phase II/III trials (ongoing and planned) will test the proof of concept of overcoming endocrine resistance with combination of some molecular agent with hormonal therapy as backbone. The targeted agents will target inhibitors of TORC1, HER2, EGFR, IGF-1R, protein kinase C-β/PDK1/p70S6K, and farnesyl transferase [61,76].

The only completed study in this regard is the Breast Cancer Trials of Oral Everolimus-2 (BOLERO-2) study. BOLERO-2 study randomized hormone sensitive Her-2 negative postmenopausal women with refractory disease to letrozole or anastrazole to exemestane with or without everolimus. Trial achieved its primary endpoint of progression free survival (6.9 vs. 2.8 months, HR, 0.43, p = 0.0043). Patients on combination arm showed significantly improved response to treatment as well (p <0.001) [78]. However, the results of the overall survival were disappointing, and there was no statistically significant advantage of using everolimus with exemestane. Everolimus was associated with toxicity including stomatitis, interstitial lung disease and hyperglycemia and hypertriglyceridemia.

PMW with HRP, Her2 negative MBC with previous exposure to AIs were randomized to tamoxifen with or without everolimus in the TAMRAD (Tamoxifen plus Everolimus) study. Patients in the combination arm achieved better response (61% vs. 42%, p = 0.045) and TTP (8.6 vs. 4.5 months, HR, 0.54, p = 0.002) [79].

The TAnDEM (Trastuzumab and Anastrozole Directed against ER-Positive HER2-Positive Mammary Carcinoma) tested anastrazole with or without trastuzumab as primary treatment in hormone receptor and Her2 positive women with MBC. Women assigned to combined modality had better progression free survival (p = 0.0016) but no difference in OS was seen. This was most likely due to the cross-over of 70% of patients from anastrazole arm [80]. Another trial assessed letrozole as single agent or in combination with lapatininb as primary treatment for women with hormone responsive Her2 positive MBC. Combination therapy resulted in improved PFS as compared to the single agent (HR, 0.71, p = 0.019) [81].

Conclusion

Hormonal treatment has proven efficacy for HRP breast cancer in all treatment settings. Tamoxifen is the standard of care for premenopausal women in neo-adjuvant and adjuvant setting. Women who become postmenopausal after 5 years of tamoxifen can be switched to 5 years of AIs. Extended use of Tamoxifen to 10 years and OFS with AIs are beginning to be considered as alternative to 5 years of adjuvant tamoxifen. For post-menopausal women, 5 years of AIs, or switch therapy, or extended use of AIs following 2-5 years of tamoxifen is the standard of care. For patients with metastatic breast cancer, AIs remain the gold standard. Addition of fulvestrant to AIs has produced equivocal results. Drug resistance to anti-estrogens is an emerging problem, one trial has shown advantage in progression free survival, but not in overall survival, and many other options are being tested in multiple trials.

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