Endocrine therapy in metastatic breast cancer: a closer look at the current clinical practice

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Endocrine therapy is a very effective and well tolerated approach in the treatment of hormone receptor positive metastatic breast cancer. Endocrine therapy has shown comparable results to chemotherapy with regard to survival rates, and therefore, it is recommended in the initial treatment of metastatic breast cancer, except in patients with rapidly progressive disease, where chemotherapy is needed. We have several options of endocrine therapy in first and subsequent lines of treatment in premenopausal and postmenopausal women with metastatic breast cancer, and there has been a great progress in the development of newer agents and combinations. There are few unanswered questions that are raised in the current clinical practice, and more studies are needed to answer them in order to have a better insight of how we may best use endocrine therapy before we need to use chemotherapy. This article will review the current options of treatment and highlight those questions.

A 68-year-old African American woman was diagnosed with a locally advanced, estrogen receptor-positive (ER-positive), progesterone receptor-positive (PgR-positive), and human epidermal growth factor receptor 2 (HER2) nonamplified right breast cancer, stage IIIC (pT2pN3M0). She underwent a right mastectomy, followed by adjuvant chemotherapy with doxorubicin and cyclophosphamide followed by paclitaxel and adjuvant radiotherapy to the chest wall. She was started on adjuvant endocrine therapy with anastrozole. After 18 months of anastrozole, she presented with left shoulder and low back pain. A nuclear medicine bone scintigraphy showed increased activity in the left shoulder along the coracoid process and in multiple thoracolumbar vertebrae. A magnetic resonance imaging (MRI) scan of the spine and left shoulder confirmed multiple osseous metastases in the left shoulder and vertebrae. A computed tomography scan of the patient's chest and abdomen did not show any evidence of visceral metastases. What are the best systemic treatment options in first and subsequent lines of therapy for this patient?

This article reviews the current available options and advances in endocrine therapies for metastatic breast cancer (MBC) in premenopausal and postmenopausal women and discusses the unanswered questions and points of controversies on the topic. In the last decade, there have been many advances in the endocrine therapy options for MBC, although many questions still need to be answered.

Background

Breast cancer is the most frequently diagnosed cancer in women, representing 14.0% of all new cancer cases in the United States.[1] With the development of the multidisciplinary team approach, the newer surgical techniques, and the incorporation of adjuvant and neoadjuvant therapy including chemotherapy, endocrine therapy, anti-HER2 targeted therapy, and radiation therapy, recurrence rates have declined. However, about 20%-30% of patients who receive an initial diagnosed of early-stage, nonmetastatic breast cancer will still have a recurrence with a distant metastatic disease, and 6%-10% of new breast cancer cases present initially as stage IV, which is referred to as de novo MBC.

Although MBC is not a curable disease, with the advancements in systemic therapies, cytotoxic therapy, endocrine therapy, and anti-HER2 therapy, there has been a significant improvement in survival among these patients. [2-4] Systemic therapy for the hormone receptor-positive (HR-positive) – the ER- and/or PgR-positive MBC –includes endocrine therapy and cytotoxic chemotherapy.

The combination of chemotherapy and endocrine therapy has not shown any added benefit, but increased toxicity, and therefore it is not recommended.[5] A meta-analysis of 6 trials (692 women) that compared endocrine therapy with chemotherapy in MBC showed that chemotherapy resulted in higher response rates (RR, 1.25, 1.01-1.54, *P*

= .04), but that failed to be interpreted to a clear overall survival(OS) benefit (hazard ratio [HR], 0.94; 95% confidence index [CI], 0.79-1.12; P = .5).[6] Although this meta-analysis was done more than 10 years ago, the findings are still strongly endorsed in current clinical practice. So, initial treatment with endocrine therapy is recommended except in patients with rapidly progressive disease, where chemotherapy is needed for an immediate clinical response. This is usually followed by a transition to endocrine therapy after a good response and/or a stable disease has been achieved. Chemotherapy is also indicated after progression on, or after a becoming resistance to endocrine therapy. Although no end point have been shown to be a surrogate for overall survival in MBC,[7] progression-free survival (PFS) has been generally accepted as the primary end point in most of the clinical trials investigating endocrine therapy in MBC, because most patients will likely receive many subsequent agents after progression, including other endocrine agents and/or chemotherapy.

Premenopausal women
Options of endocrine therapy in MBC in premenopausal women include the selective estrogen receptor modulator (SERM), tamoxifen, and ovarian suppression or ablation with or without an aromatase inhibitor. Ovarian ablation can be accomplished with oophorectomy or ovarian radiation with resulting permanent amenorrhea and menopause. Ovarian function may be also suppressed with gonadotropin-releasing hormone (GnRH) analogs, such as goserelin, leuprolide, or triptorelin. This may be associated with long-term health effects in young women, including cardiovascular disease, hot flashes, vaginal dryness, sexual dysfunction, joint pain, and decrease in bone density.

Ovarian suppression with a GnRH analog is equivalent to ovarian ablation (HR, 0.80; 95% CI, 0.53-1.20; P = .006).[8] Early data have shown that tamoxifen and ovarian ablation are equivalent,[9] and the combination of tamoxifen and ovarian suppression is superior to ovarian suppression alone; OS (P = .02; HR, 0.78) and PFS (P = .0003; HR, 0.70).[10] Aromatase inhibitors (AIs) are contraindicated in premenopausal women because they may initiate a negative feedback to the pituitary gland and increase estrogen production in the ovaries. AIs have been shown to be safe in premenopausal women when they are given after ovarian ablation or ovarian suppression by a GnRH analog. A phase 2 trial by Carlson and colleagues showed an antitumor activity of the combination of anastrozole and goserelin in premenopausal women with HR-positive MBC.[11] A South Korean trial in women with HR-positive MBC compared the combination of letrozole and goserelin in 35 premenopausal women with letrozole in 38 postmenopausal women, and reported comparable efficacies in both arms with regard to time to progression (TTP) (9.5 months

[95% CI, 6.4-12.1 months] vs 8.9 months [95% CI, 6.4-13.3 months], respectively).[12] No clinical trials have compared the combination of ovarian suppression alone with the combination of ovarian suppression and an AI.

The common practice in the United States is to start treatment with tamoxifen or the combination of tamoxifen and ovarian suppression, and to switch to an AI after ovarian ablation as a second line. For women who do not wish to have oophrectomy or ovarian suppression, the only other second-line option is cytotoxic chemotherapy. Enrolling in clinical trials is always recommended.

Postmenopausal women
In postmenopausal women, there are more options including, AIs, tamoxifen, fulvestrant, everolimus, and the new cyclin-dependent kinase 4/6 (CDK 4/6) inhibitor, palbociclib. AIs have been proven to be superior to tamoxifen in OS. Mouridsen and colleagues have shown that patients treated with letrozole demonstrated a longer median survival compared with those who were treated with tamoxifen (34 months vs 30 months, respectively), and a longer time to chemotherapy (16 months vs 9 months, P = .005).[13] In a meta-analysis of 23 trials by Mauri and colleagues, OS improved more with AIs than with tamoxifen (relative hazard, 0.87; 95% CI, 0.82-0.93; P < .001).[14] There are 3 available AIs – 2 nonsteroidals, anastrozole and letrozole; and a steroidal, exemestane.

Fulvestrant, an ER-blocking agent that may overcome tamoxifen resistance, was compared with tamoxifen in first-line endocrine therapy in postmenopausal women with advanced breast cancer, and there was no significant difference in TTP (6.8 vs 8.3 months, respectively; HR, 1.18; 95% CI, 0.98-1.44; P = .088).[15] The dose of fulvestrant used in that trial was 250 mg intramuscular (IM) monthly. The CONFIRM trial compared 2 different doses of fulvestrant, 250 mg and 500 mg; both were given on days 0, 14, 28, then every 28 days thereafter. Median OS was 26.4 months for fulvestrant 500 mg and 22.3 months for 250 mg (HR, 0.81; 95% CI, 0.69-0.96; P = .02).[16] The FIRST trial compared first-line fulvestrant at the 500 mg dose with anastrozole and reported a similar clinical benefit rate (75% vs 67%, respectively; odds ratio, 1.30; 95% CI, 0.72-2.38; P = .386) and a similar objective response rate, (36% vs 35.5%), but TTP was significantly longer for fulvestrant compared with anastrozole (median TTP not reached for fulvestrant vs 12.5 months for anastrozole; HR, 0.63; 95% CI, 0.39-1.00; P = .0496).[17] The FALCON trial, a phase 3 trial comparing fulvestrant with anastrozole in first-line treatment of ER-positive MBC has completed accrual, and results are pending. The combination of fulvestrant and anastrozole in first-line endocrine therapy was compared with anastrozole alone in 2 clinical trials, the FACT trial and the SWOG S0226. On the one hand, the European FACT trial showed

no difference in TTP between the combination arm (n = 258) and anastrozole arm (n = 256) (10.8 vs 10.2 months; HR, 0.99; 95% CI, 0.81-1.20; P = .91).[18] On the other hand, the S0226 findings suggested that combination therapy was better in PFS (15 vs 13.5 months; HR, 0.80; 95% CI, 0.68-0.94; P = .0007) and in OS (47.7 vs 41.3 months; HR, 0.81; 95% CI, 0.65-1.00; P = .05).[19]

The mammalian target of rapamycin (mTOR) pathway plays a central role in proliferation and apoptosis, and can be activated by a range of signaling factors including ERs and other growth factors, which suggests mTORs may be helpful in extending the benefits of endocrine therapy. This was demonstrated in the BOLERO-2, a phase 3 trial comparing placebo and exemestane with everolimus and exemestane in postmenopausal women with HR-positive MBC who progressed on anastrozole or letrozole. At 18 months follow-up, the median PFS was 3.19 months in the placebo arm and 7.82 months in the everolimus arm (HR, 0.45, 95% CI, 0.38-0.54; P < .0001).[20] The TAMRAD trial, a French GINECO study, demonstrated that the combination of tamoxifen and everolimus was superior to tamoxifen alone in clinical benefit rate, TTP, and OS in postmenopausal women.[21]

The CDK 4/6 inhibitors inhibited ER-positive breast cancer cells in preclinical studies by causing G1 cell cycle arrest. In the PALOMA-1, a phase 2 trial, the combination of letrozole and the CDK 4/6 inhibitor, palbociclib, almost doubled PFS from 10.2 months to 20.2 months, compared with letrozole alone (HR, 0.488; 95% CI, 0.319-0.748; P = .0004) in first-line endocrine therapy of postmenopausal women with ER-positive MBC.[22] In February 2015, the US Food and Drug Administration (FDA) approved palbociclib in combination with letrozole in first-line endocrine treatment of postmenopausal women with ER-positive and HER2 nonamplified MBC.[23]

The most common adverse effects reported with the combination were neutropenia, fatigue, pulmonary embolism, and fatigue. Grade 3/4 neutropenia was reported in 54% of patients in the palbociclib arm, but no cases of febrile neutropenia were reported. The results of PALOMA-2, a phase 3 trial comparing palbociclib plus letrozole and letrozole in first-line treatment of postmenopausal women with advanced breast cancer, are pending. The PALOMA-3, a double blind, phase 3 trial of fulvestrant with or without palbociclib in premenopausal and postmenopausal women with HR-positive, HER2-negative MBC that progressed on prior endocrine therapy was stopped early after meeting its primary end point. The PALOMA-3 results, which were presented at the 2015 ASCO annual meeting, demonstrated significant PFS advantage of the addition of palbociclib (9.2 vs 3.8 months [HR, 0.422; 95% CI, 0.318- 0.560; P < .000001]).[24] There are 2 other CDK 4/6 inhibitors, LEE 011 and abemaciclib (LY2835219),

are being evaluated in combination with an AI or fulvestrant in ER-positive breast cancer.

There are other investigational agents that have been explored in combination with endocrine therapy (Table). Entinostat, a novel class I histone deacetylase inhibitor, inhibits growth factor signaling pathways that mediate AI resistance and resensitize tumors to AIs. The ENCORE 301 trial compared the combination of exemestane and entinostat with exemestane and placebo in MBC after failure of nonsteroidal AI, and noted that the entinostat arm was superior in PFS (4.28 vs 2.27 months [HR, 0.73; 95% CI, 0.49-1.09; P = .06 by stratified log-rank test, 1-sided]).[25] Although the difference in PFS was only 2 months, it should be noted that the trial enrolled heavily treated patients, most of whom had received prior chemotherapy either in the adjuvant or metastatic setting. Androgen receptor (AR) expression is observed in some of the ER-positive breast cancers. Preclinical studies have indicated that enzalutamide, an AR inhibitor, suppresses estradiol-mediated proliferation of ER-positive, AR-positive breast cancer cells.[26] A randomized phase 2 trial of exemestane with or without enzalutamide is in progress in women with advanced ER-positive, HER2 nonamplified advanced breast cancer. Other investigational agents, including the selective estrogen receptor down regulators (SERDs), that can potentially degrade ER mutations and the phophatidyleinositol-3-kinase (PI3K) inhibitors that target the PI3K pathway are being investigated.

Until recently, the common practice was to use an AI as first line. The second and third line options may include fulvestrant, the combination of exemestane and everolimus, or tamoxifen. After the FDA approval of palbociclib in first line, its use in combination with letrozole in first-line treatment has been suggested. Palbociclib has not yet been approved for second-line endocrine therapy, but after the recent results PALMOA-3 trial, the combination of fulvestrant and palbociclib has been suggested as an effective second-line treatment option. With regards to the introductory clinical case presented, the patient progressed while receiving adjuvant anastrozole, and therefore, we treated her with fulvestrant. Few months later, she progressed on fulvestrant, and we started her on the combination of exemestane and everolimus.

Questions and controversies
Premenopausal women
Although the combination of tamoxifen and ovarian suppression has been shown to be superior to ovarian suppression alone,[10] it has not been demonstrated whether the combination of tamoxifen and ovarian ablation is superior to tamoxifen alone. The 2 options are currently acceptable given the lack of any study comparing them to each other.

It is worth noting that most MBC patients are post-

TABLE Investigational endocrine therapy approaches in hormone receptor-positive metastatic breast cancer

Agent	Study name, phase	Arms	No. of patients	Prior therapy	Results
Entinostat (HDAC inhibitor)	ENCORE 301, phase 2 Yardley et al	exemestane+placebo vs exemestane+entinostat	66 64	Endocrine tx and/or chemotx allowed	PFS, 2.27 mo PFS, 4.28 mo
ARN (GDC)-810 (ER mutation target)	NCT01823835, phase 1/2	GDC-810	Actively recruiting	Endocrine tx and/or chemotx allowed	na
Buparlisib (Pan-PI3K inhibitor BKM 120)	BELLE-2, phase 3 Iwata et al	fulvestrant+BKM 120 vs fulvestrant+placebo	1,148 enrolled	AI and mTOR allowed	na
Buparlisib (Pan-PI3K inhibitor BKM 120)	BELLE-3, phase 3 Iwata et al	fulvestrant+BKM 120 vs fulvestrant+placebo	420 estimated	AI and 1 chemotx allowed	na
Enzalutamide (AR blockade)	NCT02007512, phase 2	exemestane+enzalutamide vs exemestane+placebo	247	1 endocrine tx and 1 chemotx allowed	na

AI, aromatase inhibitors; AR, androgen receptor; ER, estrogen receptor; HDAC, histone deacetylase; mTOR, mammalian target of rapamycin; na, not available; PFS, progression-free survival; tx, therapy

menopausal, and in the remaining premenopausal minority, HR-negative breast cancer is more common.[27] So, there are only a relatively small number of premenopausal women with HR-positive MBC, and that may explain the difficulty in accruing this population in randomized clinical trials.

Another point that is worth exploring is whether or not it is feasible to extrapolate the data from the postmenopausal trials and apply them to premenopausal women after ovarian suppression. There are many effective treatment options available to postmenopausal women, and if we were able to answer this question, we may have more options available to premenopausal women before submitting them to cytotoxic chemotherapy. For example, the European FACT trial, which compared the combination of letrozole and fulvestrant with letrozole alone in the first-line treatment of postmenopausal women with MBC, has exceptionally enrolled premenopausal women after ovarian suppression with a GnRH agonist. The answer of this question becomes more imperative after the development of the novel CDK 4/6 inhibitors and their exciting results in postmenopausal women.[22] The PALOMA-3 trial enrolled premenopausal women after ovarian suppression with goserelin,[24] and in a subgroup analysis, both premenopausal and perimenopausal women (HR, 0.44; 95% CI, 0.32-0.83) and postmenopausal women (HR, 0.41; 95% CI, 0.30-0.56) had similar benefit (*P* value for interaction, 0.94). That raises the question as to whether we can use the data from PALOMA-1 and treat premenopausal women with the combination of palbociclib and letrozole

in first-line endocrine therapy after ovarian suppression by a GnRH agent.

Postmenopausal women

There is some uncertainty about the use of the steroidal AI, exemestane, after failure of a nonsteroidal AI, anastrozole or letrozole. In a systemic review of 9 studies by Beresford and colleagues, the clinical benefit of exemestane after treatment failure of a nonsteroidal AI in MBC ranged from 12% to 55%.[28] The EFFECT trial demonstrated that exemestane and fulvestrant, at a loading dose of 500 mg IM on day 0, 250 mg on days 14 and 28, and 250 mg every 28 days thereafter, are equally active in postmenopausal women with advanced breast cancer who have experienced progression or recurrence during treatment with a nonsteroidal AI (TTP, 3.7 months in both groups [HR, 0.963; 95% CI, 0.819-1.133; *P* = .6531]).[29]

It is debatable whether or not the combination of fulvestrant and an AI is superior to an AI alone in first-line MBC treatment. As already mentioned here, 2 trials, FACT and SWOG S0226, resulted in inconsistent outcomes.[18,19] Although that question may be no longer significant after the development of the CDK 4/6 inhibitor, palbociclib, and its preferable use in combination with letrozole as a first-line treatment, it may remain valid for those who cannot get the new drug because of its cost or toxicity, particularly severe neutropenia. It is worth mentioning that the S0226 trial had more patients presenting as de novo metastatic disease, while the FACT trial had more patients who had received adjuvant chemotherapy and adjuvant

tamoxifen. The SoFEA trial showed that the combination of fulvestrant (500 mg day 1, and 250 mg days 15 and 29, and every 28 days thereafter) and anastrozole seems to be of no additional advantage over fulvestrant or exemestane alone as a second-line treatment after a nonsteroidal AI (median PFS, 4.4 months with fulvestrant plus anastrozole, 4.8 months with fulvestrant plus placebo, and 3.4 months with exemestane; HR, 1.00; 95% CI, 0.83-1.21; P = .98).[30]

The various options of treatment in postmenopausal women are creating more questions with regard to the optimal sequence of treatment. Moreover, after progression on first-line palbociclib and letrozole, we do not know if the available second-line options are still effective. Fulvestrant and the combination of everolimus and exemestane were studied after failure of an AI. So, will be they still effective after the CKD 4/6 inhibitors?

As reported in the PALOMA-3, the combination of palbociclib and fulvestrant in second-line endocrine therapy is very effective, and we are waiting to find out whether this combination will be approved as a second line. It is also interesting to investigate whether this robust antineoplastic activity of the CKD 4/6 inhibitors is comparable with cytotoxic chemotherapy in the rapidly progressive disease, thus delaying or even sparing the use of chemotherapy.

HR-positive, HER2 amplified MBC

Although most of the studies in HR-positive MBC in the last decade enrolled HER2 nonamplified patients, the coexpression of HR, and HER2 is not uncommon, and about half of the HER2 amplified breast cancers will also coexpress HRs. These patients are usually treated initially with chemotherapy and HER2-directed agent. After achieving a good response and/or a stable disease, continuing with a HER2 agent and adding endocrine agent have been of interest.

Despite the early data that suggested that HER2 overexpression confers intrinsic resistance to hormonal treatment,[31,32] 2 trials showed that the combination of anti-HER2 and endocrine therapy was superior to endocrine therapy alone in HR-positive and HER2 amplified MBC. The TAnDEM trial demonstrated that PFS improved more with trastuzumab in combination with anastrozole than with anastrozole alone (median PFS, 4.8 vs 2.4 months [HR, 0.63; 95% CI, 0.47-0.84; P = .0016]).[33] There was no statistically significant OS difference; however, 70% of patients in the anastrozole alone arm crossed over to receive trastuzumab after progression. Another trial by Johnston and colleagues compared the combination of lapatinib and letrozole with letrozole alone, and demonstrated significantly reduced risk of disease progression with the combination arm (median PFS, 8.2 vs 3.0 months [HR, 0.71; 95% CI, 0.53-0.96; P = .019]).[34] There is a difference in opinion about the combination

of anti-HER2 and endocrine therapy in HR-positive and HER2 amplified MBC. The National Comprehensive Cancer Network does not recommend such a combination, although some experts believe that the combination is a valid option and should be considered in individualized clinical settings.[35]

Summary

Endocrine therapy is well tolerated and fairly effective in treating HR-positive MBC, and there has been a great success in developing new active endocrine agents. However, there are a few questions that need to be answered, and some debates that need to be resolved. More options of endocrine therapy may be available to premenopausal women provided that ovarian suppression is achieved before submitting them to cytotoxic chemotherapy. We need more data to define the best sequence and combinations of the currently available agents to postmenopausal women. The new novel CDK 4/6 inhibitors are very promising, and we hope to have more information on how we can best use them. The debate over combining endocrine therapy to anti-HER2 agents in HR-positive, HER2 amplified MBC needs to be addressed. More promising investigational agents targeting the ER pathway such as the AR inhibitors, SERDs and the PI3K inhibitors are on the horizon.

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