Endocrine Treatment of Breast Cancer: Current Perspectives, Future Directions

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ABSTRACT
Breast cancer remains one of the major causes of death in women, and endocrine treatment is currently one of the mainstay of treatment in patients with estrogen receptor positive breast cancer. Endocrine therapy either slows down or stops the growth of hormone-sensitive tumors by blocking the body’s capability to yield hormones or by interfering with hormone action. In this paper, we intended to review various approaches of endocrine treatments for breast cancer highlighting successes and limitations. There are three settings where endocrine treatment of breast cancer can be used: neoadjuvant, adjuvant, or metastatic. Several strategies have also been developed to treat hormone-sensitive breast cancer which include ovari...
chances of developing breast cancer.8,10,15 Treating breast cancer involve multidisciplinary approach – diagnostic imaging, pathology, medical oncology, surgery and radiation oncology16,17 – which reduces the prevalence and incidence of this fatal disease in long term16,18-23. In this paper, we intended to review various approaches of endocrine treatments for breast cancer highlighting successes and limitations.

**Treatment of Breast Cancer**

Treatment for breast cancer is dependent on disease stage, histologic and molecular subtypes and menopausal status32. Further characteristics persuading treatment choice for early breast cancer embrace harmonizing the risk of relapse with the benefit of intervention and patient factors such as the effect of treatment on fertility24. Surgery (either mastectomy or breast-conserving surgery with or without axillary lymph node dissection) and radiotherapy take part an imperative role in early breast cancer. Systemic pharmacological interventions are used for almost all women and the principal treatment strategies for those with advanced breast cancer25-29.

**Biological Subtype of Breast Cancer: Implications For Endocrine Therapy**

Breast cancer is a heterogeneous complex of diseases with many subtypes having distinct biological features30. Different subtypes have various treatment approaches with different clinical outcomes. The activated receptors of hormone-sensitive breast cancer cells cause transform in the expression of specific genes acting as stimuli of cell growth. Breast cancer is divided into three molecular subtypes, each of which has a direct link on treatment choices31. The first group, estrogen receptor (ER) expression positivity and/or progesterone receptor (PgR) positivity, lacks over-expression or amplification of HER2 (human epidermal growth factor). The second group is characterized by over-expression or amplification of HER2, with more than half of these tumors also positive for expression of ER/PgR. The third group lacks expression of ER, PgR, and HER2, and is thus referred to as triple negative breast cancer. Approximately 65% of newly diagnosed breast cancers are ER/PgR-positive and HER2-negative (sometimes referred to as luminal tumors), while an additional 20% of newly diagnosed cases are HER2-positive. Endocrine therapy is considered as the mainstay for treatment of these patients. Hormonally targeted drugs, specifically drugs that antagonize estrogen binding to the ER, drugs that block estrogen biosynthesis, and drugs that antagonize and down-regulate the ER, have been the main mode of systemic treatment for patients with both localized and metastatic ER/PgR-positive breast cancers. ER positive breast cancer is less aggressive than HER2-positive or triple negative breast cancer32,33. The endocrine treatment of breast cancer is discussed in detail in a subsequent section of the paper.

**Father Of Endocrine Ablation In Cancer Management**

Colonel Sir George Thomas Beatson (1848-1933), a renowned British physician, was an innovator in the field of Oncology to evolve a new treatment strategy for breast cancer and has been called the ‘father of endocrine ablation in cancer management’34. Sir George Thomas Beatson’s treatment of oophorectomy for advanced breast cancer resulted in estrogen deprivation to ER positive breast cancer and known for over 100 years35,36. In 1895, George Thomas Beatson performed the first bilateral salpingo-oophorectomy (BSO) on a young patient with recurrent inoperable breast cancer37. It was noted that eight months later all loco-regional disease had disappeared38. This endocrine treatment is the first targeted therapy in the history of ER positive breast cancer38,39.

**Settings Of Endocrine Treatment Of Breast Cancer**

There are three settings where endocrine treatment of breast cancer can be used: neoadjuvant,40 adjuvant,41,42 or metastatic43-45. Doses of endocrine treatment is the same for all settings and it does not vary with age, body surface area or weight.

**Neoadjuvant Setting**

The neoadjuvant therapy reduces the size of breast tumor adequately to facilitate for effective breast conserving surgery,46 the approach is considered as a reasonable treatment option for localized ER+ breast cancer47. It focuses on primary cancer in breast in situ apart from breast +/-auxiliary lymph nodes involvement of ipsilateral/same side48,49. This is curative intent and usually aimed at postmenopausal women who are unable to tolerate chemotherapy for other co-morbidity or wishes to spare chemotherapy for their side-effects or not fit or willing for surgery. Endocrine treatment works slowly hence aggressive or rapid growing tumors should not be combated with this treatment47. Young women with grade 1 tumor or very indolent breast cancer should be treated by a skilled and experienced oncologist and monitored carefully51,52 as treatment failure may be devastating for the patient who may be cured by an alternative treatment. Mastectomy may be recommended when breast conserving surgery is not possible owing to tumor size, multifocal disease, aesthetically unfavorable ratio of breast size to tumor volume, or at the patient’s request53,54. Data from randomized controlled trials have shown that neoadjuvant hormone therapies - in particular, aromatase inhibitors - can be effective in reducing the size of breast tumors in postmenopausal women55,56,57. The results in premenopausal women are uncertain as more trials need to be conducted58.

**Adjuvant Setting**

Adjuvant treatment plan is the administration of added medical intervention after surgery +/- after chemotherapy to extinguish or impede micro-metastases. Primary surgery for breast cancer is either wide local excision or mastectomy and sentinel lymph node biopsy +/- axillary lymph node clearance. Whole-breast radiotherapy for women who has had wide local excision and radiotherapy also indicated in some cases after mastectomy59. Adjuvant therapies (AT) is aimed to prevent the cancer relapsing by eradicating micro-metastatic disease. AT can start after chemotherapy if chemotherapy is planned after surgery or if the patient does not required chemotherapy then directly after the surgery59. Research has given away that women who accept at least 5 years of AT therapy with
Several strategies have been developed to treat hormone-sensitive breast cancer, including the following:

**Blocking Ovarian Function**

Ovarian ablation is a process where estrogen levels in women can be reduced by eliminating or suppressing ovarian function\(^55,76\). Methods of irreversible ovarian ablation include surgical oophorectomy and ovarian irradiation. Ovarian function can also be suppressed temporarily by drugs - gonadotropin-releasing hormone (GnRH) agonists\(^77,78\). The ovarian suppression drugs include gonadotropin-releasing hormone (GnRH) agonists i.e. goserelin and leuprolide\(^57,79\). These drugs interfere with signals from the pituitary gland that stimulate the ovaries to produce estrogen.

**Blocking Estrogens Production**

Blocking the estrogen receptor is one of the oldest and most effective strategic methods of treating breast cancer\(^55,80,81\). Aromatase interfere with the body's ability to produce estrogen from androgens by blocking aromatase enzyme activity\(^55,56\). Aromatase inhibitors are used in the treatment of breast cancer in postmenopausal women\(^66,82\). However, these drugs can be used in premenopausal women if they are given together with a drug that suppresses ovarian function\(^83,81\). Examples of aromatase inhibitors are anastrozole and letrozole, both of which temporarly inactivate aromatase, and exemestane, which permanently inactivates the enzyme\(^83\).

**Blocking Estrogen's Effects**

A number of drugs interfere with estrogen’s ability to stimulate the growth of breast cancer cells: Selective estrogen receptor modulators (SERMs): Examples of SERMs are tamoxifen, raloxifene, and toremifene. These drugs block the effects of estrogen in the breast tissue and the tissue failed to receive estrogen's signals to grow and multiply\(^82,84,85\). SERMs have the ability to bind to estrogen receptors throughout the body and act as estrogen agonists or antagonists depending upon the target organ. For example, Tamoxifen blocks the effects of estrogen in breast tissue but acts like estrogen in the uterus and bone\(^86,88\). Other antiestrogen drugs: Fulvestrant blocks the receptors and stops estrogen reaching the cancer cells which slows down or blocks the cells from multiplication\(^87\). In addition, when fulvestrant binds to the estrogen receptor, the receptor is targeted for destruction of cancer cells\(^87,88\).

**Pharmacological Interventions in Breast Cancer**

Numerous endocrine agents have been developed in recent years: estrogens, androgens, progestins, antiestrogens [SERMs and selective estrogen receptor down regulators (SERDs)], aromatase inhibitors, gonadotropin-releasing hormone (GnRH) analogs, antiprogestins and antiandrogens\(^89\). Though endocrine treatments is very effective treatment for ER+ breast cancer but primary or secondary endocrine resistance is a huge issue. Recent advances in ER-positive cancers include combination treatment of AIs therapy with everolimus (a mtor inhibitor) or palbociclib (CDK4/6 inhibitor); a large number of clinical trials are...
investigating other mechanisms of overcoming endocrine therapy including drug resistance. Selective Estrogen Receptor Modulators (SERMs) SERMs are synthetic non-steroidal agents that bind to the ER and stimulate or inhibit target sites throughout the body. Tamoxifen, the pioneering SERM, is one of the most effective treatments for breast cancer which acts by competing with estrogen to bind to ER in breast cancer cells. Tamoxifen weakly binds with ER receptors in the breast cell and stop the dimerization process; hence killing the cancer cell. It has an antagonist effect on breast cancer cells and it has agonist or estrogen like effects on other organs such as on bone, endometrium and cholesterol. Tamoxifen has been found to be very active when it used as a principal method in previously untreated patients and as a second and third line treatment after endocrine therapy and chemotherapy. Tamoxifen produces estrogen like effect it is protective to bone and does not cause osteoporosis. Also, it reduces cholesterol and by that reduces heart attack. Evidences suggest tamoxifen can increase possibility endometrial cancer, pulmonary embolism, stroke, deep vein thrombosis, cataracts, hormonal symptoms, and sexual problems — even though the serious risks are rare. The use of 5 years of adjuvant tamoxifen would produce an absolute 15-year endometrial cancer risk of about 2-3%, and that use of 10 years rather than 5 years of tamoxifen would produce an additional risk by year 15 of about 2%. Tamoxifen can be used in neoadjuvant setting on premenopausal or postmenopausal women to shrink the tumor. In HR- positive patients, tamoxifen reduces both breast cancer recurrence (47%) and mortality (26%) . It also can be used in pre-invasive cancer that is ductal cancer in situ after appropriate local therapy. Tamoxifen used to prevent breast cancer in women both premenopausal and post-menopausal who already treated for breast cancer in curative intent in adjuvant setting. It is also used in stage 4 breast cancer for long duration as long as cancer responding to treatment and with tolerable side effects. Finally, it can be used in patient with strong family history of breast cancer.

A daily dose of Tamoxifen is a 20-mg tablet and patients taking anti-depressant (CYP2D6 inhibitors) can reduce effect of Tamoxifen. Tamoxifen is drug should not be taken while breast feeding and not be pregnant on tamoxifen as it has teratogenic effects on fetus and especially on first trimester. Patients who are on Tamoxifen in an adjuvant setting and wish to be pregnant should come out of Tamoxifen at least 3 months before trying pregnancy after discussions with their oncologists. Premenopausal women who remain premenopausal after completion of 5 years of Adjuvant Tamoxifen will advised to continue 5 years more as it has been observed in a study that ER positive tumors tend to relapse after stopping Tamoxifen. Women who is premenopausal and on Tamoxifen become postmenopausal can be switched from Tamoxifen to Letrozole once they have menopause and this is sequential treatment with letrozole and tamoxifen.

Tamoxifen is now considered as the adjuvant treatment of choice after aromatase inhibitor for postmenopausal patients who need endocrine treatment. This correlation is seen in premenopausal patients treated with oophorectomy or tamoxifen, and in postmenopausal patients treated with tamoxifen.

Aromatase Inhibitors (AIs)
Aromatase, also called estrogen synthetase or estrogen synthase, is an enzyme responsible for a key step in the biosynthesis of estrogens. AIs inhibits estrogen synthesis, and without estrogen ER within cancer cell cannot be activated hence cancer cell cannot proliferate and eventually cells more likely to die. There are three AIs which include anastrozole, exemestane, and letrozole. AIs are a class of drugs used in the treatment of breast cancer in postmenopausal women and gynecomastia in men.

AIs can be used in pre-invasive cancer that is ductal carcinoma in situ after appropriate local treatment. They can also be used in neoadjuvant setting to shrink the tumor, adjuvant settings where patient is already treated for breast cancer and aromatase inhibitors can be used in curative intent that prevents the cancer to coming back. AIs are also used in stage 4 breast cancer. Also have similar side-effects like Tamoxifen those are hot flashes, night sweats, fatigue, voice changes, loss of libido, nausea, mood irritability, weight gain but hot flashes and night sweats are more pronounce on Tamoxifen. Most specific side-effects of AIs are pain of small joints, joint stiffness and muscle aches. Bone loss (osteopenia and osteoporosis) are common on aromatase inhibitors hence appropriate monitoring and investigations are necessary.

AIs (Letrozole 2.5 mg, Exemestane 25 mg or Anastrozole 1 mg) is to be taken daily. Many trials have shown superiority of Aromatase Inhibitor (AI) over Tamoxifen in postmenopausal women to prevent relapse. Previously it was recommended 5 years of adjuvant aromatase inhibitor to prevent relapse of breast cancer but recent MA17 trial shown light on extended aromatase inhibitor treatment to prevent relapse as estrogen receptor positive tumor showing tendency to relapse up to 20 years after initial treatment is over.

Gonadotropin-releasing Hormone Agonist (GnRH)
GnRH agonists (e.g. goserelin, nafarelin and leuprorelin) are increasingly being used for the treatment of breast cancer in women with functioning ovaries. GnRH agonists suppress ovarian function, inducing artificial menopause in premenopausal women. As AIs cannot block the amount of estrogen produced by ovaries in premenopausal women, the source need to be block either by Goserelin monthly injections or removal of ovaries surgically. Routinely, Goserelin injection are used 4 weeks prior to commencing any aromatase inhibitor and another Goserelin injection is required once every 4 weeks to continue if patient is on aromatase inhibitors.

Selective estrogen receptor down-regulators (SERDs)
SERDs (e.g. Fulvestrant) bind to the estrogen receptor (ER) and induce the rapid down-regulation of ER.
Fulvestrant is a pure antiestrogen and binds strongly with ER$^{128}$. It blocks estrogen to get into cancer cell, and estrogen receptor without estrogen has got no ability to couple or dimerize. Like Tamoxifen it has got no agonist effect on other tissue$^{128}$. Fulvestrant is usually used in metastatic setting that is for stage 4 breast cancer$^{129}$. In adjuvant setting, Fulvestrant can sometimes use where Tamoxifen is contraindicated for blood clot history or aromatase inhibitors for osteoporosis$^{130}$. It is administered with an intramuscular injection of 500 mg every 4 weeks after initial 3 injections within 4 weeks$^{128}$. It is well tolerated$^{31}$ but like any other anti-estrogen treatment it can cause: hot flushes, night sweats, mood swings, nausea, and abdominal pain and voice changes$^{132}$. Fatigue can be experienced but these are still very mild in comparison to any other anti-estrogen medication$^{81}$. Extra precautions need to be taken by the patients who are on low molecular weight heparin or oral anticoagulation$^{133,134}$. It is best to avoid Fulvestrant as it can cause intramuscular bleeding.

**Endocrine Therapy for Breast Cancer: Premenopausal Vs. Postmenopausal Women**

Breast cancer is one of the leading cause of cancer related mortality in premenopausal women. The endocrine treatments for premenopausal patients’ include tamoxifen with or without ovarian suppression/ovarian ablation, an AIs with ovarian suppression/ovarian ablation, or ovarian suppression/ovarian ablation alone$^{110,135-137}$. Premenopausal women ER and/or PR-positive breast cancers can be benefited with tamoxifen for five years$^{58,138}$. However, breast cancer may recur in women of any age by almost 50%$^{78}$. It was also demonstrated that Tamoxifen helps reduce the risk of developing a new breast cancer in the contralateral breast$^{40}$. In women younger than 35-40 years, combined endocrine therapy with tamoxifen can be used for ovarian suppression on a temporary basis$^{31}$.

In postmenopausal women, use of a nonsteroidal aromatase inhibitor or tamoxifen should be considered as small amounts of estrogen are produced by the adrenal glands, fatty tissue and even breast tissue after menopause. AIs reduce the levels of estrogen in the body$^{58,80}$. These drugs first became available in the mid-to-late 1990s and have been shown to reduce the risk of breast cancer recurrence in postmenopausal women with early stage breast cancer. In trials for patients with advanced and endocrine responsive disease, the use of either anastrozole or letrozole has been shown to yield some advantage in terms of treatment outcome as compared with tamoxifen$^{121,141}$. The use of other drugs, such as high-dose progestins or Megestrol acetate may follow as a third-line or last line of endocrine treatment to the patients who donot have any other option of endocrine or chemotherapy treatment or not fit of chemotheraytreatmentand these drugs increase appetite and uplift mood. Postmenopausal women with ER-positive tumors may do just as well or perhaps a bit better with an AIs when compared to tamoxifen$^{142}$. It is not recommended for these women to undergo ovarian suppression as adjuvant treatment since their ovaries are not producing estrogen$^{143}$. Oophorectomy would be considered in this case in women who are BRCA 1 or 2 mutation carriers or have a strong family history of ovarian cancer as a preventive measure$^{10,144}$. Patients who are diagnosed with early stage non-invasive ductal carcinoma in situ (DCIS) may be given tamoxifen to prevent breast cancer from occurring in the unaffected breast$^{145}$. In summary, anastrozole offers another option for postmenopausal women with ER-positive DCIS, and the choice between it and tamoxifen will probably depend more on previous history of other conditions and short-term tolerability than differences in efficacy$^{146}$.

**CONCLUSION**

Breast cancer remains the leading cause of death in women. Despite of the success of the endocrine therapies in reducing the disease recurrence and overall increasing survival, 20-25% of patients receiving adjuvant tamoxifen or aromatase inhibitors will have relapse in 10 years of the initiation of the treatment$^{147}$. As estrogen triggers activation of ER, the main stem of endocrine treatment for breast cancer is either removal of estrogen (it can be done by targeting of the ER receptor) or stopping synthesis of estrogen in ER positive breast cancer. The concept that changing the hormonal balance of the patient with breast cancer could lead to changes in tumor growth and regression of metastatic disease. Endocrine treatment has major therapeutic value in patients with estrogen receptor positive breast cancer. Endocrine treatments are cheap and have a fixed single daily dose for all ages, heights and weights of patients. It is generally well-tolerated though small groups of women may experience adverse side-effects which can have impact on quality of life. Nevertheless, these side-effects can be mitigated by switching between treatments and by available interventions. Endocrine treatments are not nearly as toxic as chemotherapy and frequent hospitalization can be avoided. It has been demonstrated that these medicines are likely to provide greater benefit than chemotherapy. Recent treatment approach became apparent that extended adjuvant hormonal therapy is beneficial to both node +/- patients. Unfortunately, the quality of life is significantly affected by the adjuvant endocrine therapies leading to poor quality of life, low compliance and treatment continuation rate.

New targeted therapy are now under investigation to demonstrate ‘substantially longer progression-free survival’ in patients with advanced HR+ and HER2-negative breast cancer$^{148}$. Researchers are excited with findings of clinical trials with CDK4/6 inhibitors e.g. palbociclib, ribociclib and abemaciclib$^{149}$. These drugs have the potential to improve the efficacy of endocrine therapy including overcoming the resistance$^{148}$. A clinical trial noted a progression-free survival of approximately 10 months with palbociclib. Ribociclib, recently approved by the FDA, also showed strong efficacy in the treatment of breast cancer. However, the overall goals for breast cancer including endocrine therapy should focus on effective control of cancer, design personalized medical therapeutic approach, increase survival time and quality...
of life, and improve supportive and palliative care for end-stage disease.

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