Available online on www.ijpqa.com
International Journal of Pharmaceutical Quality Assurance 2017; 8(3); 92-103
doi: 10.25258/ijpqa.v8i03.9570
ISSN 0975 9506

Review Article

Endocrine Treatment of Breast Cancer: Current Perspectives, Future Directions

Tazia Irfan[1], Mainul Haque[2*], Sayeeda Rahman[3], Russell Kabir[4], Nuzhat Rahman[5], Md. Anwarul Azim Majumder[6]

[1]*Royal Marsden Hospital, Chelsea, London, UK.*
[2]*Unit of Pharmacology, Faculty of Medicine and Defense Health' National Defense University of Malaysia, Kem Sungai Besi, 57000 Kuala Lumpur, Malaysia.*
[3]*Department of Clinical Sciences, School of Pharmacy and Medical Sciences, Faculty of Life Sciences, University of Bradford, UK.*
[4]*Department of Medical Science and Public Health, Faculty of Medical Sciences, Anglia Ruskin University, Bishop Hall Lane, Chelmsford, Essex, UK.*
[5]*University of Alabama at Birmingham, Comprehensive Cancer Center, Birmingham, Alabama, USA.*
[6]*Faculty of Medical Sciences, The University of the West Indies, Cave Hill Campus, Barbados, West Indies.*

Received: 27th July, 17; Revised:19th August, 17; Accepted:25th August, 17; Available Online:25th September, 2017

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 ovarian ablation, blocking estrogen production, and stopping estrogen effects. Selective estrogen-receptor modulators (SERMs) (e.g. tamoxifen and raloxifene), aromatase inhibitors (AIs) (e.g. anastrozole, letrozole and exemestane), gonadotropin-releasing hormone agonists (GnRH) (e.g. goserelin), and selective estrogen receptor downregulators (SERDs) (e.g. fulvestrant) are currently used drugs to treat breast cancer. Tamoxifen is probably the first targeted therapy widely used in breast cancer treatment which is considered to be very effective as first line endocrine treatment in previously untreated patients and also can be used after other endocrine therapy and chemotherapy. AIs inhibit the action of enzyme aromatase which ultimately decrease the production of estrogen to stimulate the growth of ER+ breast cancer cells. GnRH agonists suppress ovarian function, inducing artificial menopause in premenopausal women. Endocrine treatments are cheap, well-tolerated and have a fixed single daily dose for all ages, heights and weights of patients. Endocrine treatments are not nearly as toxic as chemotherapy and frequent hospitalization can be avoided. New drugs in preliminary trials demonstrated the potential for improvement of the efficacy of endocrine therapy including overcoming resistance. 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.

Keywords: Breast cancer, endocrine treatment, premenopausal women, postmenopausal women.

INTRODUCTION

Globally breast cancer is the furthermost common identified cancer among women, with nearly 1.7 million new cases diagnosed in 2012 and at large it is the second most common cancer. This represents about 12% of all new cancer cases; one quarter of all cancers in women and leading cause of death among all cancer deaths[1-3]. Breast cancer is common in both developed and developing countries – 52% of new cases and 62% of deaths happen in low-economy countries[4]. There are multiple risk factors for breast cancer, which include old age, genetic mutations, having dense breasts**,** exposure to radiation during early age**,** family history of breast cancer**,** early minerache, late menopause**,** late or no pregnancy, lack of physical activity, being overweight or obese after menopause, hormone replacement therapy, oral contraceptives, drinking alcohol etc[5-8]. Overall 5-10% breast cancers are inherited[9] and approximately 5% of patients inherit a high-penetrance cancer-predisposing gene[10-14]. Inherited cases of breast cancer are associated with following genes: BRCA1, BRCA2, CHEK2, ATM, FGFR2 and TOX3[8,10]. Mutations in BRCA1 and BRCA2 are considered as the strongest breast cancer predictors and mutations in one of these genes have a 40-80%

**Author for Correspondence: runurono@gmail.com*

chances of developing breast cancer[8,10,15]. Treating breast cancer involve multidisciplinary approach – diagnostic imaging, pathology, medical oncology, surgery and radiation oncology[16,17] – which reduces the prevalence and incidence of this fatal disease in long term[16,18-23]. 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 status[24]. 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 fertility[24]. 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 cancer[25-29].

Biological Subtype of Breast Cancer: Implications For Endocrine Therapy

Breast cancer is a heterogeneous complex of diseases with many subtypes having distinct biological features[30]. 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 stimulus of cell growth. Breast cancer is divided into three molecular subtypes, each of which has a direct link on treatment choices[31]. 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 cancer[32,33]. 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 years[35,36]. In 1895, George Thomas Beatson performed the first bilateral salpingo-oophorectomy (BSO) on a young patient with recurrent inoperable breast cancer[37]. It was noted that eight months later all loco-regional disease had disappeared[38]. This endocrine treatment is the first targeted therapy in the history of ER positive breast cancer[38,39].

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 metastatic[43-45]. 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 cancer[47]. It focuses on primary cancer in breast *in situ* apart from breast +/-auxiliary lymph nodes involvement of ipsilateral/same side[48,49]. 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 combatted with this treatment[50]. Young women with grade 1 tumor or very indolent breast cancer should be treated by a skilled and experienced oncologist and monitored carefully[51,52] 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 request[53,54]. 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 women[55,56,57]. The results in premenopausal women are uncertain as more trials need to be conducted[55].

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 clearence. Whole-breast radiotherapy for women who has had wide local excision and radiotherapy also indicated in some cases after mastectomy[58]. 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 surgery[58]. Research has given away that women who accept at least 5 years of AT therapy with

tamoxifen after having surgery for early-stage ER-positive breast cancer have reduced risks of breast cancer relapse, including a new breast cancer in the other breast, and death at 15 years[59]. Tamoxifen has been permitted by the US Food and Drug Administration (FDA) for adjuvant hormone treatment of premenopausal and postmenopausal women (and men) with ER-positive early-stage breast cancer, and anastrozole and letrozole have been officially permitted for the use in postmenopausal women[55].

Until recently, most women who received adjuvant hormone therapy to reduce the chance of a breast cancer recurrence took tamoxifen every day for 5 years[55]. Multiple studies and meta-analysis revealed that the superiority of the third-generation aromatase inhibitors (letrozole, anastrozole and exemestane) and now prescribed as alternatives to tamoxifen as first-line therapy because of improved efficacy and safety margin in postmenopausal women with ER-positive advanced breast cancer. Although these agents do not affect mortality rate of breast cancer patients[60-64]. Thereafter, with the advent of newer hormone therapies, some of which have been compared with tamoxifen in clinical trials, additional approaches to hormone therapy have become popular[65-67]. As for instance, some women may take an aromatase inhibitor daily for 5 years, instead of tamoxifen. Other group receive added medication with an aromatase inhibitor after 5 years of tamoxifen. The last group of women change to an aromatase inhibitor after 2-3 years of tamoxifen, for a total of 5 or more years of hormone therapy. Decisions about the type and duration of adjuvant hormone therapy must be made on an individual basis[65-67]. This complex decision-making process is best carried out by an oncologist.

Metastatic setting (or stage 4 cancer)

In metastatic breast cancer (Stage IV or advanced breast cancer), the treatment aims to stop further spread of cancer and if possible to shrink the tumor though in this setting a cure is not possible. Sometimes in a metastatic setting, endocrine treatment is also used as a maintenance therapy after the response achieved from chemotherapy (by stablization or shrinkage). Hormone therapy work by preventing the cancer cells from getting the estrogen they need to grow and the choice of hormone therapy depends on menopausal status and any past hormone treatment for early breast cancer[68-71].

Studies have shown that tamoxifen is effective in treating women and men with metastatic breast cancer[72]. The antiestrogen fulvestrant can be used in postmenopausal women with metastatic ER-positive breast cancer after treatment with other antiestrogens[73]. The aromatase inhibitors anastrozole and letrozole can be given to postmenopausal women as initial therapy for metastatic hormone-sensitive breast cancer[74,75] These two drugs, as well as other the aromatase inhibitor exemestane, can also be used to treat postmenopausal women with advanced breast cancer whose disease has worsened after treatment with tamoxifen[60].

Approaches of Endocrine Treatment of Breast Cancer

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[55,79]. These drugs interfere with signals from the pituitary gland that stimulate the ovaries to produce estrogen.

Blocking Estrogen 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[56,82] However, these drugs can be used in premenopausal women if they are given together with a drug that suppresses ovarian function[55,81]. Examples of aromatase inhibitors are anastrozole and letrozole, both of which temporarily 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[85,86].

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[90].

Selective Estrogen Receptor Modulators (SERMs)

SERMs are synthetic non-steroidal agents that bind to the ER and stimulate and 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[91]. Tamoxifen weakly binds with ER receptors in the breast cell and stop the dimerization process; hence killing the cancer cell[92]. 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[91,92]. Tamoxifen produces estrogen like effect it is protective to bone and does not cause osteoporosis[93,94]. Also, it reduces cholesterol and by that reduces heart attack[95]. 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[96-98]. The use of 5 years of adjuvant tamoxifen would produce an absolute 15-year endometrial cancer risk of about 2-3%,[59] and that use of 10 years rather than 5 years of tamoxifen would produce an additional risk by year 15 of about 2%[99].

Tamoxifen can be used in neoadjuvant setting on premenopausal or postmenopausal women to shrink the tumor[46]. In HR- positive patients, tamoxifen reduces both breast cancer recurrence (47%) and mortality (26%)[100]. 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[55,81]. It is also used in stage 4 breast cancer for long duration as long as cancer responding to treatment and with tolerable side effects[55,101]. Finally, it can be used in patient with strong family history of breast cancer[102].

A daily dose of Tamoxifen is a 20-mg tablet and patients taking anti-depressant (CYP2D6 inhibitors) can reduce effect of Tamoxifen[103,104]. 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[105,106]. 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[107]. 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[99,108]. 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[109,110]. Tamoxifen is now considered as the adjuvant treatment of choice after aromatease inhibitor for postmenopausal patients who need endocrine treatment[51]. This correlation is seen in premenopausal patients treated with oophorectomy or tamoxifen, and in postmenopausal patients treated with tamoxifen[51,80].

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[111,112]. 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[113].

AIs can be used in pre-invasive cancer that is ductal carcinoma *in situ* after appropriate local treatment[114]. 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[115]. AIs are also used in stage 4 breast cancer[116-119]. AIs 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[120]. 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[121,122].

AIs (Letrozole 2.5 mg, Exemestane 25 mg or Anastrozole 1 mg) is to be taken daily[123]. Many trials have shown superiority of Aromatase Inhibitor (AI) over Tamoxifen in postmenopausal women to prevent relapse[56,109]. 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[124,125].

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[76]. 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[76]. 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[126,127].

Selective estrogen receptor down-regulators (SERDs)

SERDs (e.g. Fulvestrant) bind to the estrogen receptor (ER) and induce the rapid down-regulation of ER[128].

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[131] 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[138,139]. However, breast cancer may recur in women of any age by almost 50%[51]. It was also demonstrated that Tamoxifen helps reduce the risk of developing a new breast cancer in the contralateral breast[140]. In women younger than 35-40 years, combined endocrine therapy with tamoxifen can be used for ovarian suppression on a temporary basis[51].

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[56,80]. 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 is 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.

REFERENCES

1. World Cancer Research Fund International. Breast cancer statistics. Available at http://www.wcrf.org/int/cancer-facts-figures/data-specific-cancers/breast-cancer-statistics [Accessed on May 9-2017].
2. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J. Cancer.* 2015;136(5):E359-386. Doi: 10.1002/ijc.29210.
3. Servick K. Breast cancer: a world of differences. *Science* 2014;343(6178):1452-1453. DOI: 10.1126/science.343.6178.1452.
4. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics. 2012. *CA Cancer J Clin*. 2015;65:87-108.
5. Centre for Disease Control and Prevention. What Are the Risk Factors for Breast Cancer? U.S. Department of Health & Human Services, 1600 Clifton Road Atlanta, GA 30329-4027 USA. 2016. Available at https://www.cdc.gov/cancer/breast/basic_info/risk_factors.htm [Accessed on May 9-2017].
6. Memorial Hospital of Converse County. Memorial Hospital of Converse County – Mammography. 111 S. 5th Street, Douglas, Wyoming 82633. Available at https://conversehospital.com/services/womens-health-center/memorial-hospital-of-converse-county-mammography/ [Accessed on May 9-2017].
7. Howell A, Anderson AS, Clarke RB, Duffy SW, Evans DG, Garcia-Closas M, Gescher AJ, Key TJ, Saxton JM, Harvie MN. Risk determination and prevention of breast cancer. *Breast Cancer Res.* 2014;16(5):446. Doi:10.1186/s13058-014-0446-2.
8. Mavaddat N, Antoniou AC, Easton DF, Garcia-Closas M. Genetic susceptibility to breast cancer. *Mol Oncol*. 2010;4(3):174-191. Doi: 10.1016/j.molonc.2010.04.011.
9. Jardines L, Goyal S, Fisher P, Weitzel J, Royce M, Goldfarb SB. Breast Cancer Overview: Risk Factors, Screening, Genetic Testing, and Prevention. 2015. Available at file:///C:/Users/user/Downloads/Cancer_Network_-_Breast_Cancer_Overview_Risk_Factors_Screening_Genetic_Testing_and_Prevention_-_2015-06-11%20(2).pdf [Accessed on May 11-2017].
10. Petrucelli N, Daly MB, Pal T. BRCA1- and BRCA2-Associated Hereditary Breast and Ovarian Cancer. 1998 Sep 4 [Updated 2016 Dec 15]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2017.
11. Bogdanova N, Helbig S, Dörk T. Hereditary breast cancer: ever more pieces to the polygenic puzzle. *Hered Cancer in Clin Pract*. 2013;11(1):12. Doi:10.1186/1897-4287-11-12.
12. Apostolou P, Fostira F. Hereditary Breast Cancer: The Era of New Susceptibility Genes. *BioMed Res. Int.* 2013;2013:747318. Doi:10.1155/2013/747318.
13. Nagy R, Sweet K, Eng C. Highly penetrant hereditary cancer syndromes. *Oncogene*. 2004;23(38):6445-6470. Doi: 10.1038/sj.onc.1207714.
14. Hodgson S. Mechanisms of inherited cancer susceptibility. *J Zhejiang Univ Sci B*. 2008; 9(1):1-4. Doi:10.1631/jzus. B073001.
15. Ripperger T, Gadzicki D, Meindl A, Schlegelberger B. Breast cancer susceptibility: current knowledge and implications for genetic counselling. *Eur J Hum Genet*. 2009; 17(6):722-731. doi:10.1038/ejhg.2008.212.
16. Boileau JF, Simmons C, Clemons M, et al. Extending neoadjuvant care through multi-disciplinary collaboration: proceedings from the fourth annual meeting of the Canadian Consortium for Locally Advanced Breast Cancer. *Curr Oncol*. 2012;19(2):106-114. Doi:10.3747/co.19.1045.
17. McDonald ES, Clark AS, Tchou J, Zhang P, Freedman GM. Clinical Diagnosis and Management of Breast Cancer. *J Nucl Med*. 2016;57(Suppl 1):9S-16S. Doi: 10.2967/jnumed.115.157834.
18. Bodai BI, Tuso P. Breast Cancer Survivorship: A Comprehensive Review of Long-Term Medical Issues and Lifestyle Recommendations. *Perm J*. 2015;19(2):48-79. Doi:10.7812/TPP/14-241.
19. Chopra I, Chopra A. Follow-up care for breast cancer survivors: improving patient outcomes. *Patient Relat Outcome Meas*. 2014;5:71-85. Doi:10.2147/PROM.S49586.
20. Margolese, RG, Hortobagyi, GN, Buchholz, TA. The Role of Radiation for invasive Breast Cancer. In: Kufe DW, Pollock RE, Weichselbaum RR, et al., editors. Holland-Frei Cancer Medicine. 6th edition. Hamilton (ON): BC Decker; 2003. Available at: https://www.ncbi.nlm.nih.gov/books/NBK13034/ [Accessed May 11-2017].
21. National Institute for Clinical Excellence (NICE). Guidance on Cancer Services Improving Outcomes in Breast Cancer. Manual Update. 2002. Available at https://www.nice.org.uk/guidance/csg1/resources/improving-outcomes-in-breast-cancer-update-773371117 [Accessed May 11-2017].
22. Saskatchewan Cancer Agency. Breast Cancer Treatment Guidelines. 2012. Available at http://www.saskcancer.ca/Breast%20CPGs%2005-12%20revised [Accessed May 11-2017].
23. Sarfati D, Koczwara B, Jackson C. The impact of comorbidity on cancer and its treatment. *CA Cancer J Clin*. 2016;66(4):337-350. Doi: 10.3322/caac.21342.
24. Di Leo A, Curigliano G, Diéras V, Malorni 4, Sotiriou C, Swanton C, Thompson A, Tutt A, Piccart M. New approaches for improving outcomes in breast cancer in Europe. *Breast*. 2015;24(4):321-330. Doi: 10.1016/j.breast.2015.03.001.

25. Goldhirsch A, Wood WC, Coates AS, Gelber RD, Thurlimann B, Senn HJ. Panel members. Strategies for subtypes-dealing with the diversity of breast cancer: highlights of the St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011. *Ann Oncol*. 2011; 22: 1736e47.
26. Aebi S, Davidson T, Gruber G, Cardoso F; ESMO Guidelines Working Group. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2011; 22 (Suppl 6): vi12-24. Doi: 10.1093/annonc/mdr371.
27. Aebi S, Davidson T, Gruber G, Castiglione M; ESMO Guidelines Working Group. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2010;21 (Suppl 5): v9-14. Doi: 10.1093/annonc/mdq159.
28. Gonzalez-Angulo AM, Morales-Vasquez F, Hortobagyi GN. Overview of Resistance to Systemic Therapy in Patients with Breast Cancer. In: Madame Curie Bioscience Database [Internet]. Austin (TX): Landes Bioscience; 2000-2013. Available at: https://www.ncbi.nlm.nih.gov/books/NBK6306/ [Accessed on May 18-2017].
29. Gonzalez-Angulo AM1, Morales-Vasquez F, Hortobagyi GN. Overview of resistance to systemic therapy in patients with breast cancer. *Adv Exp Med Biol*. 2007;608:1-22.
30. Polyak K. Heterogeneity in breast cancer. *J Clin Invest*. 2011 Oct 3; 121(10): 3786–3788.
31. Sorlie, T, Perou, C., Tibshirani, R., Aas, T., Geisler, S., Johnsen, H., *et al* (2001). Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. *Proceedings of the National Academy of Sciences*, 10869-10874.
32. Alluri P, Newman L. Basal-like and Triple Negative Breast Cancers: Searching for Positives Among Many Negatives. *Surg Oncol Clin N Am* 2014; 23(3): 567-577.
33. Bae SY, Kim S, Lee JH, Lee HC, Lee SK, Kil WH, Kim SW, Lee JE, Nam SJ. Poor prognosis of single hormone receptor- positive breast cancer: similar outcome as triple-negative breast cancer. *BMC Can* 2015; 15:138.
34. Arafah BM. Sir George Thomas Beatson, M.D. (1848-1933). *J Lab Clin Med* 1987; 109(3): 373-4.
35. Stockwell S. Classics in Oncology George Thomas Beatson MD (1848-1933). *CA Cancer J Clin.* 1983; 33(2): 105-21.
36. Singh G. Oophorectomy in Breast Cancer—Controversies and Current Status. *Indian J Surg* 2012; 74(3): 210-212.
37. Beatson GT. On the treatment of inoperable cases of carcinoma of the mamma: suggestions for a new method of treatment, with illustrative cases. *Lancet.* 1896; 148 (3803): 162-165.
38. Park W-C. Role of Ovarian Function Suppression in Premenopausal Women with Early Breast Cancer. *J Breast Cancer* 2016; 19(4): 341-348.
39. Scharl A, Salterberg A. Significance of Ovarian Function Suppression in Endocrine Therapy for Breast Cancer in Pre-Menopausal Women. *Geburtshilfe Frauenheilkunde*. 2016; 76(5): 516-524.
40. Teshome M, Hunt KK. Neoadjuvant therapy in the treatment of breast cancer. *Surg Oncol Clin N Am.* 2014; 23(3): 505-523.
41. Rao RD, Cobleigh MA. Adjuvant endocrine therapy for breast cancer. *Oncology*. 2012; 26(6): 541-7.
42. Iino Y, Takei H, Morishita Y. Adjuvant endocrine therapy for breast cancer. *Gan To Kagaku Ryoho* 1995; 22 (Suppl 1):81-7.
43. Rugo HS, Rumble RB, Macrae E, Barton DL, Connolly HK, Dickler MN, Fallowfield L, Fowble B, Ingle JN, Jahanzeb M, Johnston SRD, Korde LA, Khatcheressian JL, Mehta RS, Muss HB, Burstein HJ. Endocrine Therapy for Hormone Receptor–Positive Metastatic Breast Cancer: American Society of Clinical Oncology Guideline. *J Oncol Pract.* 2016; 12(6): 583-7.
44. Reinert T, Barrios CH. Optimal management of hormone receptor positive metastatic breast cancer in 2016. *Ther Adv Med Oncol*. 2015; 7(6): 304-320.
45. Ma CX, Dickler M. Treatment approach to metastatic hormone receptor-positive, HER2-negative breast cancer: Endocrine therapy. UpToDate. Available at https://www.uptodate.com/contents/treatment-approach-to-metastatic-hormone-receptor-positive-her2-negative-breast-cancer-endocrine-therapy [Accessed on July 1, 2017].
46. Saleh RR, Bouganim N, Hilton J, Arnaout A, Clemons M. Neoadjuvant endocrine treatment for breast cancer: from bedside to bench and back again? *Current Oncology*. 2014; 21(1): e122-e128.
47. Spring LM, Gupta A, Reynolds KL, Gadd MA, Ellisen LW, Isakoff SJ, Moy B, Bardia A. Neoadjuvant Endocrine Therapy for Estrogen Receptor–Positive Breast CancerA Systematic Review and Meta-analysis. *JAMA Oncol* 2016; 2(11): 1477-1486.
48. Zhang B-N, Cao X-C, Chen J-Y, Chen J, Fu L, Hu X-C, Jiang Z-F, Li H-L, Liao N, Liu D-G, Tao O, Shao Z-M, Sun Q, Wang S, Wang Y-S, Xu B-H, Zhang J. Guidelines on the diagnosis and treatment of breast cancer (2011 edition). *Gland Surg* 2012; 1(1): 39-61.
49. Organization for Oncology and Translational Research. 12th Annual Conference Kyoto Breast Cancer Consensus Conference 2016 International Convention. *Int J Biol Markers* 2016; 31(1): e88-99.
50. Pearlman AW. Breast cancer--influence of growth rate on prognosis and treatment evaluation: a study based on mastectomy scar recurrences. *Cancer*. 1976 Oct;38(4):1826-3.
51. Christinat A, Di Lascio S, Pagani O. Hormonal therapies in young breast cancer patients: when, what and for how long? *J Thorac Dis* 2013; 5(Suppl 1): S36-S46.
52. Brouckaert O, Wildiers H, Floris G, Neven P. Update on triple-negative breast cancer: prognosis and

management strategies. *Int J Womens Health* 2012; 4: 511-520.
53. Buggi F, Curcio A, Falcini F, Folli S. Multicentric/Multifocal Breast Cancer: Overview, Biology, and Therapy. In: Eds. Schatten H. Cell and Molecular Biology of Breast Cancer, Springer Science, Humana Press, New York, USA, 2013, pp. 29-42.
54. Fajdic J, Djurovic D, Gotovac N, Hrgovic Z. Criteria and Procedures for Breast Conserving Surgery. *Acta Inform Med* 2013; 21(1): 16-19.
55. US Department of Health and Human Services, National Institutes of Health, National Cancer Institute. Hormone Therapy for Breast Cancer. 2017. Available at https://www.cancer.gov/types/breast/breast-hormone-therapy-fact-sheet#q2 [Accessed on July 1, 2017].
56. Fabian CJ. The what, why and how of aromatase inhibitors: hormonal agents for treatment and prevention of breast cancer. *Int J Clin Prac* 2007;61(12):2051-2063.
57. Barroso-Sousa R, Silva DDAFR, Alessi JVM, Mano MS. Neoadjuvant endocrine therapy in breast cancer: current role and future perspectives. *Ecancermedicalscience* 2016;10: 609.
58. Chew HK. Adjuvant therapy for breast cancer: who should get what? *West J Med* 2001; 174(4): 284-287.
59. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomized trials. *Lancet* 2011; 378(9793): 771-784.
60. Mauri D, Pavlidis N, Polyzos NP, Ioannidis JP. Survival with aromatase inhibitors and inactivators versus standard hormonal therapy in advanced breast cancer: meta-analysis. *J Natl Cancer Inst* 2006; 98 (18): 1285-91.
61. Dowsett M, Cuzick J, Ingle J, Coates A, Forbes J, Bliss J, Buyse M, Baum M, Buzdar A, Colleoni M, Coombes C, Snowdon C, Gnant M, Jakesz R, Kaufmann M, Boccardo F, Godwin J, Davies C, Peto R. Meta-analysis of breast cancer outcomes in adjuvant trials of aromatase inhibitors versus tamoxifen. *J Clin Oncol* 2010; 28 (3): 509-18.
62. Bonneterre J, Buzdar A, Nabholtz JM, Robertson JF, Thürlimann B, von Euler M, Sahmoud T, Webster A, Steinberg M; Arimidex Writing Committee; Investigators Committee Members. Anastrozole is superior to tamoxifen as first-line therapy in hormone-receptor positive advanced breast carcinoma. *Cancer* 2001; 92 (9): 2247-58.
63. Mouridsen H, Gershanovich M, Sun Y, Pérez-Carrión R, Boni C, Monnier A, Apffelstaedt J, Smith R, Sleeboom HP, Jänicke F, Pluzanska A, Dank M, Becquart D, Bapsy PP, Salminen E, Snyder R, Lassus M, Verbeek JA, Staffler B, Chaudri-Ross HA, Dugan M. Superior efficacy of letrozole versus tamoxifen as first-line therapy for postmenopausal women with advanced breast cancer: results of a phase III study of the International Letrozole Breast Cancer Group. *J Clin Oncol* 2001; 19 (10):2596-606.
64. Nabholtz JM, Buzdar A, Pollak M, Harwin W, Burton G, Mangalik A, Steinberg M, Webster A, von Euler M. Anastrozole is superior to tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: results of a North American multicenter randomized trial-Arimidex Study Group. *J Clin Oncol* 2000;18(22):3758-67.
65. Untch M, Thomssen C. Clinical practice decisions in endocrine therapy. *Cancer Invest* 2010;28(Suppl 1):4-13.
66. Regan MM, Neven P, Giobbie-Hurder A, Goldhirsch A, Ejlertsen B, Mauriac L, Forbes JF, Smith I, Láng I, Wardley A, Rabaglio M, Price KN, Gelber RD, Coates AS, Thürlimann B; BIG 1-98 Collaborative Group; International Breast Cancer Study Group (IBCSG). Assessment of letrozole and tamoxifen alone and in sequence for postmenopausal women with steroid hormone receptor-positive breast cancer: the BIG 1–98 randomized clinical trial at 8.1 years median follow-up. *Lancet Oncol* 2011; 12(12):1101-8.
67. Burstein HJ, Griggs JJ. Adjuvant hormonal therapy for early-stage breast cancer. *Surg Oncol Clin N Am* 2010; 19(3):639-647.
68. Gradishar WJ, Anderson BO, Balassanian R, Blair SL, Burstein HJ, Cyr A, Elias AD, Farrar WB, Forero A, Giordano SH, Goetz M, Goldstein LJ, Hudis CA, Isakoff SJ, Marcom PK, Mayer IA, McCormick B, Moran M, Patel SA, Pierce LJ, Reed EC, Salerno KE, Schwartzberg LS, Smith KL, Smith ML, Soliman H, Somlo G, Telli M, Ward JH, Shead DA, Kumar R. Invasive Breast Cancer Version 1.2016, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2016; 14(3): 324-54.
69. Gradishar WJ, Anderson BO, Balassanian R, Blair SL, Burstein HJ, Cyr A, Elias AD, Farrar WB, Forero A, Giordano SH, Goetz M, Goldstein LJ, Hudis CA, Isakoff SJ, Marcom PK, Mayer IA, McCormick B, Moran M, Patel SA, Pierce LJ, Reed EC, Salerno KE, Schwartzberg LS, Smith KL Smith ML, Soliman H, Somlo G, Telli M, Ward JH, Shead DA, Kumar R. NCCN Guidelines Insights Breast Cancer, Version 1.2016. *J Natl Compr Canc Netw.* 2015; 13(12): 1475-85.
70. Bevers TB, Anderson BO, Bonaccio E, Buys S, Daly MB, Dempsey PJ, Farrar WB, Fleming I, Garber JE, Harris RE, Heerdt AS, Helvie M, Huff JG, Khakpour N, Khan SA, Krontiras H, Lyman G, Rafferty E, Shaw S, Smith ML, Tsangaris TN, Williams C, Yankeelov T; National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: breast cancer screening and diagnosis. *J Natl Compr Canc Netw*. 2009; 7(10): 1060-96.
71. Gradishar W, Salerno KE. NCCN Guidelines Update: Breast Cancer. *J Natl Compr Canc Netw*. 2016; 14(5 Suppl): 641-4.

72. Sawka CA, Pritchard KI, Shelley W, DeBoer G, Paterson AH, Meakin JW, Sutherland DJ. A randomized crossover trial of tamoxifen versus ovarian ablation for metastatic breast cancer in premenopausal women: a report of the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) trial MA.1. *Breast Cancer Res Treat* 1997; 44(3):211–215.
73. Howell A, Pippen J, Elledge RM, Mauriac L, Vergote I, Jones SE, Come SE, Osborne CK, Robertson JF. Fulvestrant versus anastrozole for the treatment of advanced breast carcinoma: a prospectively planned combined survival analysis of two multicenter trials. *Cancer* 2005; 104(2): 236-9.
74. Cuzick J, Sestak I, Baum M, Buzdar A, Howell A, Dowsett M, Forbes JF; ATAC/LATTE investigators. Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 10-year analysis of the ATAC trial. *Lancet Oncol* 2010; 11(12):1135-1141.
75. Mouridsen H, Gershanovich M, Sun Y, Perez-Carrion R, Boni C, Monnier A, Apffelstaedt J, Smith R, Sleeboom HP, Jaenicke F, Pluzanska A, Dank M, Becquart D, Bapsy PP, Salminen E, Snyder R, Chaudri-Ross H, Lang R, Wyld P, Bhatnagar A. Phase III study of letrozole versus tamoxifen as first-line therapy of advanced breast cancer in postmenopausal women: analysis of survival and update of efficacy from the International Letrozole Breast Cancer Group. *J Clin Oncol* 2003; 21(11): 2101-9.
76. Breast Cancer Org. Ovarian Shutdown or Removal. 2016. Available at http://www.breastcancer.org/treatment/hormonal/ovary_removal [Accessed on July 2, 2017].
77. Del Mastro L, Lambertini M. Temporary Ovarian Suppression with Gonadotropin-Releasing Hormone Agonist During Chemotherapy for Fertility Preservation: Toward the End of the Debate? *Oncologist* 2015; 20(11): 1233-35.
78. Magon N. Gonadotropin releasing hormone agonists: Expanding vistas. *Indian J Endocrinol Metab* 2011; 15(4): 261-267.
79. Omar Ta, EIDidi F, Nawar WN. A potential role for sex hormone receptor antagonists in treatment of malignant salivary gland tumors, as compared to breast cancer: A review of literature. *Tanta Dent J* 2013; 10 (2): 75-85.
80. Lumachi F, Santeufemia DA, Basso SM. Current medical treatment of estrogen receptor-positive breast cancer. *World J Biol Chem* 2015; 6(3): 231-239.
81. American Cancer Society. Hormone Therapy for Breast Cancer. 2016. Available at https://www.cancer.org/cancer/breast-cancer/treatment/hormone-therapy-for-breast-cancer.html [Accessed at July 2, 2017].
82. Peng J, Sengupta S, Jordan VC. Potential of Selective Estrogen Receptor Modulators as Treatments and Preventives of Breast Cancer. *Anticancer Agents Med Chem* 2009; 9(5): 481-99.
83. Chumsri S, Howes T, Bao T, Sabnis G, Brodie A. Aromatase, Aromatase Inhibitors, and Breast Cancer. *J Steroid Biochem Mol Biol* 2011;125(1-2):13-22.
84. Maximov PY, Lee TM, Jordan VC. The Discovery and Development of Selective Estrogen Receptor Modulators (SERMs) for Clinical Practice. *Curr Clin Pharm* 2013; 8(2): 135-155.
85. Martinkovich S, Shah D, Planey SL, Arnott JA. Selective estrogen receptor modulators: tissue specificity and clinical utility. *Clin Interv Aging* 2014; 9: 1437-1452.
86. Dutertre M, Smith CL. Molecular mechanisms of selective estrogen receptor modulator (SERM) action. J Pharmacol Exp Ther 2000; 295(2): 431-7.
87. Ribas R, Pancholi S, Guest SK, Marangoni E, Gao Q, Thuleau A, Simigdala N, Polanska UM, Campbell H, Rani A, Liccardi G, Johnston S, Davies BR, Dowsett M, Martin LA. AKT Antagonist AZD5363 Influences Estrogen Receptor Function in Endocrine-Resistant Breast Cancer and Synergizes with Fulvestrant (ICI182780) In Vivo. *Mol Cancer Ther* 2015; 14(9): 2035-48.
88. Tang H, Liao Y, Zhang C, Chen G, Xu L, Liu Z, Fu S, Yu L, Zhou S. Fulvestrant-mediated inhibition of estrogen receptor signaling slows lung cancer progression. *Oncol Res* 2014; 22(1): 13-20.
89. Goldhirsch A, Colleoni M, Gelber RD. Endocrine therapy of breast cancer. *Ann Oncol* 2002; 13 (suppl_4): 61-68.
90. Hart CD, Migliaccio I, Malorni L, Guarducci C, Biganzoli L, Di Leo A. Challenges in the management of advanced, ER-positive, HER2-negative breast cancer. *Nat Rev Clin Oncol* 2015; 12(9): 541-52.
91. Legha SS, Buzdar AU, Hortobagyi GN, Wiseman C, Benjamin RS, Blumenschein GR. Tamoxifen. Use in treatment of metastatic breast cancer refractory to combination chemotherapy. *JAMA*. 1979; 242(1): 49-52.
92. Manni A, Trujillo JE, Marshall JS, Brodkey J, Pearson OH. Antihormone treatment of stage IV breast cancer. *Cancer* 1979; 43(2): 444-50.
93. Zidan J, Keidar Z, Basher W, Israel O. Effects of tamoxifen on bone mineral density and metabolism in postmenopausal women with early-stage breast cancer. *Med Oncol*. 2004; 21(2): 117-21.
94. Love RR, Mazess RB, Barden HS, Epstein S, Newcomb PA, Jordan VC, Carbone PP, DeMets DL. Effects of tamoxifen on bone mineral density in postmenopausal women with breast cancer. *N Engl J Med*. 1992; 326(13): 852-6.
95. Reis SE, Costantino JP, Wickerham DL, Tan-Chiu E, Wang J, Kavanah M. Cardiovascular effects of tamoxifen in women with and without heart disease: breast cancer prevention trial. National Surgical Adjuvant Breast and Bowel Project Breast Cancer Prevention Trial Investigators. *J Natl Cancer Inst* 2001; 93(1): 16-21.

96. Stacey D, O'Connor AM, DeGrasse C, Verma S. Development and evaluation of a breast cancer prevention decision aid for higher-risk women. *Health Expect* 2003; 6: 3-18.
97. Melnikow J, Paterniti D, Azari R, Kuenneth C, Birch S, Kuppermann M, Nuovo J, Keyzer J, Henderson S. Preferences of women evaluating risks of tamoxifen (POWER) study of preferences for tamoxifen for breast cancer risk reduction. *Cancer* 2005; 103(10): 1996-2005.
98. Metcalfe KA, Snyder C, Seidel J, Hanna D, Lynch HT, Narod S. The use of preventative measures among healthy women who carry BRCA1 or BRCA2 mutation. *Fam Cancer* 2005; 4 (2): 97-103.
99. Davies C, Pan H, Godwin J, Gray R, Arriagada R, Raina V, et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomized trial. *Lancet.* 2013; 381(9869): 805-816.
100. No authors listed. Tamoxifen for early breast cancer: an overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. *Lancet* 1998;351(9114):1451-67.
101. Chang M. Tamoxifen Resistance in Breast Cancer. *Biomol Ther* 2012;20(3):256-267.
102. National Institute for Health and Care Excellence. Major shift in breast cancer care on horizon as NICE recommends preventative drugs for 'at-risk' women. Available at http://www.nice.org.uk/newsroom/pressreleases/NICERecommendsBreastCancerdrugs.jsp. [Accessed July 3, 2017].
103. Henry NL, Stearns V, Flockhart DA, Hayes DF, Riba M. Drug Interactions and Pharmacogenomics in the Treatment for Breast Cancer and Depression. *Am J Psychiatry* 2008; 165(10): 1251-1255.
104. Lash TL, Pedersen L, Cronin-Fenton D, Ahern TP, Rosenberg CL, Lunetta KL, Silliman RA, Hamilton-Dutoit S, Garne JP, Ewertz M, Sørensen HT. Tamoxifen's protection against breast cancer recurrence is not reduced by concurrent use of the SSRI citalopram. *Br J Cancer* 2008; 99(4): 616-21.
105. Braems G, Denys H, De Wever O, Cocquyt V, Van den Broecke R. Use of Tamoxifen Before and During Pregnancy. *Oncologist* 2011; 16(11): 1547-1551.
106. Gilani S, Giridharan S. Is it safe for pregnant health-care professionals to handle cytotoxic drugs? A review of the literature and recommendations. *Ecancermedicalscience* 2014; 8: 418.
107. Koca E, Kuzan TY, Babacan T, Turkbeyler IH, Furkan S, Altundag K. Safety of Tamoxifen During Pregnancy: 3 Case Reports and Review of the Literature. *Breast Care* 2013; 8(6): 453-454.
108. National Collaborating Centre for Cancer (UK). Early and Locally Advanced Breast Cancer: Diagnosis and Treatment [Internet]. Cardiff (UK): National Collaborating Centre for Cancer (UK); 2009 Feb. (NICE Clinical Guidelines, No. 80.) 5, Adjuvant systemic therapy. Available at https://www.ncbi.nlm.nih.gov/books/NBK11632/ [Accessed July 4, 2017].
109. Schiavon G, Smith IE. Status of adjuvant endocrine therapy for breast cancer. *Breast Cancer Research* 2014; 16(2): 206.
110. Kadakia KC, Henry NL. Adjuvant Endocrine Therapy in Premenopausal Women with Breast Cancer. *Clin Adv Hematol Oncol* 2015; 13(10): 663-672.
111. Nelson LR, Bulun SE. Estrogen production and action. *J Am Acad Dermatol* 2001; 45(3 Suppl): S116-24.
112. Santen RJ, Santner SJ, Pauley RJ, Tait L, Kaseta J, Demers LM, Hamilton C, Yue W, Wang JP. Estrogen production via the aromatase enzyme in breast carcinoma: which cell type is responsible? *J Steroid Biochem Mol Biol*. 1997; 61(3-6):267-71.
113. Brodie A, Njar V, Macedo LF, Sean VT, Sabnis G. Steroidogenic Enzyme Inhibitors and Hormone Dependent Cancer. *Urol Oncol* 2009; 27(1): 53-63.
114. American Cancer Society. Treatment of Ductal Carcinoma in Situ (DCIS). 2016. Available at https://www.cancer.org/cancer/breast-cancer/treatment/treatment-of-breast-cancer-by-stage/treatment-of-ductal-carcinoma-in-situ-dcis.html [Accessed on July 5-2017].
115. Hu X, Huang W, Fan M. Emerging therapies for breast cancer. *J Hematol Oncol*. 2017; 10: 98.
116. American Cancer Society. Treatment of Stage IV (Advanced) Breast Cancer. 2016. Available at https://www.cancer.org/cancer/breast-cancer/treatment/treatment-of-breast-cancer-by-stage/treatment-of-stage-iv-advanced-breast-cancer.html [Accessed on July 6, 2017].
117. Texas Oncology. Stage Iv Breast Cancer. 2017. Available at https://www.texasoncology.com/types-of-cancer/breast-cancer/stage-iv-breast-cancer [Accessed on July 6, 2017].
118. Schneider R, Barakat A, Pippen J, Osborne C. Aromatase inhibitors in the treatment of breast cancer in post-menopausal female patients: an update. *Breast Cancer* (Dove Med Press) 2011; 3:113-125.
119. Nabholtz J-MA. Long-term safety of aromatase inhibitors in the treatment of breast cancer. *Ther Clin Risk Manag* 2008;4(1):189-204.
120. Winer EP, Hudis C, Burstein HJ, Wolff AC, Pritchard KI, Ingle JN, Chlebowski RT, Gelber R, Edge SB, Gralow J, Cobleigh MA. American Society of Clinical Oncology technology assessment on the use of aromatase inhibitors as adjuvant therapy for postmenopausal women with hormone receptor–positive breast cancer: status report 2004. *J Clin Oncol* 2005;23(3):619-29.
121. Shi Q, Giordano SH, Lu H, Saleeba AK, Malveaux D, Cleeland CS. Anastrozole-Associated Joint Pain and Other Symptoms in Patients With Breast Cancer. *J Pain* 2013; 14(3): 290-296.

122. Perez EA, Serene M, Durling FC, Weilbaecher K. Aromatase Inhibitors and Bone Loss. *Oncology (Williston Park)*. 2006; 20(9): 1029-1048.
123. Geisler J. Differences between the non-steroidal aromatase inhibitors anastrozole and letrozole – of clinical importance? *Br J Cancer*. 2011; 104(7): 1059-1066.
124. Goss PE. Preventing relapse beyond 5 years: the MA.17 extended adjuvant trial. *Semin Oncol*. 2006; 33(2 Suppl 7): S8-12.
125. Goss PE, Ingle JN, Pritchard KI, Robert NJ, Muss H, Gralow J, Gelmon K, Whelan T, Strasser-Weippl K, Rubin S, Sturtz K, Wolff AC, Winer E, Hudis C, Stopeck A, Beck JT, Kaur JS, Whelan K, Tu D, Parulekar WR. Extending Aromatase-Inhibitor Adjuvant Therapy to 10 Years. *N Engl J Med* 2016; 375:209-21.
126. Freedman OC, Fletcher GG, Gandhi S, Mates M, Dent SF, Trudeau ME, Eisen A. Adjuvant endocrine therapy for early breast cancer: a systematic review of the evidence for the 2014 Cancer Care Ontario systemic therapy guideline. *Curr Oncol* 2015; 22(Suppl 1): S95-S113.
127. Forward DP, Cheung KL, Jackson L, Robertson JFR. Clinical and endocrine data for goserelin plus anastrozole as second-line endocrine therapy for premenopausal advanced breast cancer. *Br J Cancer* 2004;90(3):590-594.
128. Osborne CK, Wakeling A, Nicholson RI. Fulvestrant: an oestrogen receptor antagonist with a novel mechanism of action. *Br J Cancer* 2004; 90(Suppl 1): S2-S6.
129. Ciruelos E, Pascual T, Arroyo Vozmediano ML, Blanco M, Manso L, Parrilla L, Muñoz C, Vega E, Calderón MJ, Sancho B, Cortes-Funes H.The therapeutic role of fulvestrant in the management of patients with hormone receptor-positive breast cancer. *Breast* 2014; 23(3): 201-8.
130. Jordan VC, Brodie AM. Development and evolution of therapies targeted to the estrogen receptor for the treatment and prevention of breast cancer. *Steroids* 2007; 72(1): 7-25.
131. Vergote I, Robertson JF. Fulvestrant is an effective and well-tolerated endocrine therapy for postmenopausal women with advanced breast cancer: results from clinical trials. *Br J Cancer* 2004; 90 (Suppl 1): S11-4.
132. Kligman L, Younus J. Management of hot flashes in women with breast cancer. *Curr Oncol* 2010;17(1):81-86.
133. Barbosa M. What is the Best Treatment for a Cancer Patient with Thrombosis? *Clin Med Insights Oncol* 2014; 8: 49-55.
134. Linkins L-A. Management of venous thromboembolism in patients with cancer: role of dalteparin. *Vasc Health Risk Manag* 2008; 4(2): 279-287.
135. Yan S, Li K, Jiao X, Zou H. Tamoxifen with ovarian function suppression versus tamoxifen alone as an adjuvant treatment for premenopausal breast cancer: a meta-analysis of published randomized controlled trials. *Onco Targets Ther* 2015; 8: 1433-1441.
136. Lambertini M, Del Mastro L, Viglietti G, Pondé NF, Solinas C, de Azambuja E. Ovarian Function Suppression in Premenopausal Women with Early-Stage Breast Cancer. *Curr Treat Options Oncol* 2017; 18(1): 4.
137. El-Saghir NS, El-Hajj II, Makarem JA, Otrock ZK. Combined ovarian ablation and aromatase inhibition as first-line therapy for hormone receptor-positive metastatic breast cancer in premenopausal women: report of three cases. *Anticancer Drugs* 2006; 17(8): 999-1002.
138. Cui X, Schiff R, Arpino G, Osborne CK, Lee AV. Biology of progesterone receptor loss in breast cancer and its implications for endocrine therapy. *J Clin Oncol*. 2005; 23(30): 7721-35.
139. Puhalla S, Brufsky A, Davidson N. Adjuvant endocrine therapy for premenopausal women with breast cancer. *Breast* 2009; 18(03): S122-S130.
140. Marchetti P, Di Rocco CZ, Ricevuto E, Bisegna R, Cianci G, Calista F, Sidoni T, Porzio G, Ficorella C. Reducing breast cancer incidence in familial breast cancer: overlooking the present panorama. *Ann Oncol* 2004; 15 (Suppl 1): I27-I34.
141. Verma S, Sehdev S, Joy A, Madarnas Y, Younus J, Roy JA. An updated review on the efficacy of adjuvant endocrine therapies in hormone receptor–positive early breast cancer. *Curr Oncol* 2009; 16(Suppl 2): S1-S13.
142. Markopoulos CJ. Minimizing early relapse and maximizing treatment outcomes in hormone-sensitive postmenopausal breast cancer: efficacy review of AI trials. *Cancer Metastasis Rev* 2010; 29(4): 581-594.
143. Cancer Net Hormonal Therapy for Early-Stage Hormone Receptor-Positive Breast Cancer. 2016. Available at http://www.cancer.net/research-and-advocacy/asco-care-and-treatment-recommendations-patients/hormonal-therapy-early-stage-hormone-receptor-positive-breast-cancer [Accessed on July 7, 2017].
144. Pruthi S, Gostout BS, Lindor NM. Identification and Management of Women With BRCA Mutations or Hereditary Predisposition for Breast and Ovarian Cancer. *Mayo Clin Proc* 2010; 85(12): 1111-1120.
145. Breast Cancer. Org. Treatment for DCIS. 2017. Available at http://www.breastcancer.org/symptoms/types/dcis/treatment [Accessed on July 7, 2017].
146. Forbes JF, Sestak I, Howell A, Bonanni B, Bundred N, Levy C, von Minckwitz G, Eiermann W, Neven P, Stierer M, Holcombe C, Coleman RE, Jones L, Ellis I. Anastrozole versus tamoxifen for the prevention of locoregional and contralateral breast cancer in postmenopausal women with locally excised ductal carcinoma in situ (IBIS-II DCIS): a double-blind, randomized controlled trial. *Lancet*. 2016;387(10021):866-873.

147. Dowsett M, Cuzick J, Ingle J, *et al.* Meta-analysis of breast cancer outcomes in adjuvant trials of aromatase inhibitors versus tamoxifen. *J Clin Oncol.* 2010;28(3):509–18. doi: 10.1200/JCO.2009.23.1274.
148. Turner N., Ro J., André F., Lois S., Verma S., Iwata H., et al. Palbociclib in hormone-receptor-positive advanced breast cancer. *N Engl J Med* 2015;373: 209–219.
149. Gradishar WJ et al. New Approaches to Endocrine Therapy for Breast Cancer. *J Natl Compr Canc Netw.* 2017;15(5S):679-681.