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Adjuvant Therapy for Early Breast Cancer

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1. Introduction

Breast cancer is the most common cause of cancer mortality among women worldwide (Key et al., 2001). There is a steady increase in the incidence of breast cancer during reproductive years with a slower rate after the age of 50 (Key et al., 2001; Collaborative Group on Hormonal Factors in Breast Cancer, 1997). Cancer of the breast is a heterogenious disease with variable response to therapy. The incidence of breast cancer among women in Europe and North America is about 2.7% by age 55, 6.3% by the age of 60, 5.0% by age 65, and about 7.7% by age 75 (Collaborative Group on Hormonal Factors in Breast Cancer, 1997). This incidence is lower in developing countries and in Japan. Risk factors for developing breast cancer include family history, early menarche, nulliparity, oral contraceptives use, late age of first pregnancy, late menopause, hormone replacement therapy, alcohol, obesity, exposure to radiation and genetics including mutations in any of *BRCA1*, *BRCA2*, *P53*, *PTEN*, and *ATM genes*. (Kelsey& Gammon, 1991; Key et al., 2001; Nittin, 1996; Børresen-Dale et al., 2010; Peto et al., 1999; Goldhirsch et al., 2009). Breast-feeding and moderate exercise have been reported to have a protective effect in some studies (Layde et al., 1989; Friedenreich et al., 1998). Tamoxifen and Raloxifen may be used in patients with increased risk for chemoprevention of breast cancer (Key et al., 2001; Visvanathan et al., 2009). A recent study have demonstrated that Exemestane use in postmenopausal women with moderately increased risk for breast cancer have significantly reduced invasive breast cancers after a median follow up of 3 years with no serious toxic effects and only minimal changes in health-related quality of life. Observational and metanalysis studies have shown some beneficial effect of Aspirin and other NSAID use in the prevention of occurrence as well as recurrence of breast cancer (Takkouche et al., 2008; Holmes et al., 2010). Diagnosis of breast cancer is considered early when the disease is detected in the breast only (T1-T3), or in the breast and locoregional lymph nodes (N1) and all detected disease can be removed surgically without spread to distant organs (e.g. bone, liver etc.).

2. Biology of breast cancer

2.1 Molecular pathology

Breast Cancer is a genetic disease. Mammary epithelial cells transform into malignant cells through a complex mechanism that involves a multistage process of sequential events of initiation, promotion, and progression at the genetic and epigenetic levels (Nittin, 1996). Premalignant lesions that increase the risk of malignant transformation include atypical

ductal hyperplasia and hyperplastic alveolar nodules (Nittin, 1996; Dupont & Page, 1985). Tamoxifen use in patients with atypical ductal hyperplasia results in a 75% risk reduction of developing invasive breast cancer (Fisher et al, 2005). Reproductive hormones are thought to influence breast cancer risk through effects on cell proliferation and DNA damage, as well as promotion of breast cancer growth. Estrogen receptor (ER) or progesterone receptor (PR)-positive and Epidermal growth factor 2, *HER- 2/neu,* overexpressing tumors account for approximately 75% and 20% of all breast cancer cases, respectively. Half of the *HER-2/neu* overexpressing breast cancers also expressing ER and, or PR receptors. About 15% of breast cancers lack expression of these three proteins and are named as triple-negative breast cancer. The hormone receptors status is used for histopathological classification of breast cancer as well as prediction of response to specific targeted therapeutic agents. Ki-67 is a marker of proliferation that is used in determining prognosis and identification of high-risk patients who may benefit From the addition of chemotherapy. Ki67-labelling index is considered low when it is < 15%, intermediate 15-30% and high when > 30%.

In the normal breast, there are three distinct types of epithelial cells: luminal or glandular cells, basal or myoepithelial cells, and stem cells. There are seven major breast cancer molecular subtypes based on patterns of gene expression and hierarchical clustering. These subtypes are: Luminal A, Luminal B, Luminal C, HER-2-enriched, Basal-like, Claudin low and Normal Breast-like group and they relate loosely to histologic and phenotypic properties and clinical outcomes.

Luminal breast cancer is called as such because of its similarity to expression of luminal breast epithelium. Luminal A tumors have the best prognosis and they make up to 40% of all breast cancers with high expression of ER-related genes, low expression of the *HER-2* cluster of genes, and low expression of proliferation-related genes (Hu et al. 2006; Voduc et al., 2010; Kennecke et al., 2010). These cells have high expression of cytokeratins 8, 18 (Perou et al., 2000). The luminal B tumors are less common and have a lower expression of ER-related genes, variable expression of Her-2 clusters and higher expression of proliferation-related genes (Voduc et al., 2010). Molecularly, a third type known as Luminal C is distinguished from luminal subtypes A and B by its high expression of a novel set of genes with unknown function, which is a feature they share with the basal-like and HER-2 subtypes (Sorlie et al., 2001). The luminal subtype B and C seem to have a worse relapse free survival and overall survival when compared to luminal A (Sorlie et al., 2001).

The *HER-2* enriched subtype is characterized by high expression of *HER-2* and proliferation genes and low expression of luminal clusters. These tumors are usually *HER-2* positive and ER/PR-negative. In the pre-*HER-2* targeted therapy era, these tumors were associated with a poorer prognosis and a higher rate locoregional as well as metastases to the brain, liver, and lung when compared with luminal A tumors. (Voduc et al., 2010; Kennecke et al., 2010)

Basal-like tumors are so called because of their similar expression to basal epithelial cells. They are typically ER/PR and *HER-2/neu* negative (triple negative) due to low expression of the luminal and HER2 gene clusters. There is a strong association between BRCA1 mutation and basal-like breast cancer (Sorlie et al., 2001). These cancers have a wide genomic instability, high expression of the proliferation cluster of genes and they are always of high grade. They also have high expression of the epidermal growth factor receptor (EGFR), p-cadherin, smooth muscle actin, c-kit, cytokeratins 5, 6, 14, and 17 (Maegawa & Tang, 2010; Perou et al 2000; Sorlie et al., 2001). Basal-like tumors are associated with high risk of locoregional relapse and a higher rate of brain, lung and distant nodal metastases with lower rate of liver and bone

metastases (Voduc et al., 2010; Kennecke et al. 2010). Luckily, these cancers are more sensitive to Anthracyclines and Taxanes (Carey et al, 2007; Maegawa & Tang, 2010).

Claudin-low is a relatively new identified subtype of breast cancer that is characterized by the low to absent expression of luminal differentiation markers, high epithelial-to-mesenchymal transition markers, immune response genes and cancer stem cell-like features (Prat et al, 2010). The majority of these tumors are ER/PR and *HER-2/neu* negative (triple negative) invasive ductal carcinomas with a high frequency of metaplastic and medullary differentiation. Their response rate to standard neoadjuvant chemotherapy is intermediate between that of basal-like and luminal tumors (Prat et al, 2010).

Normal breast-like tumors do not fall into any of these specific five types and they show high expression of many genes known to be expressed by adipose tissue and other nonepithelial cell types. These tumors also showed strong expression of basal epithelial genes and low expression of luminal epithelial genes (Sorlie et al., 2001).

Although metastatic breast cancer is beyond the scope of this chapter, it is worth mentioning that discordance in tumor characteristics (i.e., change in receptor status) between a primary breast cancer and sites of recurrence are common and re-biopsy of metastatic disease might be indicated especially if a long time has passed since the first diagnosis.

Other histologic Subtypes of breast cancer include secretory, adenoid cystic, tubular, medullary and lobular carcinomas.

2.2 Screening and testing for breast cancer

Breast cancer screening is performed in women without any signs or symptoms for early detection of breast cancer. A thorough history and detailed clinical breast examination are crucial for early detection and management of breast cancer. Symptoms or positive findings on clinical examination include a palpable lump or mass, asymmetric thickening or nodularity, nipple discharge in the absence of a palpable mass, and skin changes such as erythema, scaling, eczema, peau d'orange skin or nipple excoriation. Mammographic screening has resulted in early detection and decreased mortality from breast cancer (Humphrey et al., 2002). Ultrasonography can be a useful screening adjunct to mammography in select group of women who are young with dense breast tissue (Bevers, 2008). Breast cancer screening should be personalized and tailored to the patient age and risk factors. Asymptomatic women without any findings on physical examination should be risk stratified. Accordingly, women are either at normal or increased risk. The National Comprehensive Cancer Center (NCCN) guidelines suggest that the following women are at increased risk of breast cancer: (1) women who have previously received therapeutic thoracic or mantle irradiation; (2) women ≥ 35 years old with a 5-year risk of invasive breast carcinoma ≥1.7% using the modified Gail model (3) women with a lifetime risk of breast cancer > 20% based on models largely dependent on family history; (4) women with a strong family history or genetic predisposition; (5) women with lobular carcinoma in situ (LCIS) or atypical hyperplasia; and (6) women with a prior history of breast cancer (www.nccn.org).

Societies recommend yearly clinical breast exam (CBE) and mammograms starting at age 40 and continuing for as long as a woman is in good health. CBE every 1 to 3 years is recommended for women older than 20 and younger than 40. (Humphrey et al., 2002; Smith et al., 2003).

There is no data to support Breast self-exam (BSE) and the United States Preventive Services Task Force (USPSTF) recommends against it. Instruction in BSE has no effect on reducing breast cancer mortality (Thomas et al., 2001).

The concept of breast self-awareness, where women should know how their breasts normally look and feel-like and report any breast changes promptly to their health care provider, has been introduced over the past several years. Periodic, consistent BSE may facilitate breast self-awareness. Premenopausal women may find BSE most informative when performed at the end of menses. *A paradigm shift from SBE to breast self-awareness has been adopted over the past decade.*

Screening with a MRI in addition to mammograms should be considered for women with a lifetime risk of breast cancer >20% based on models largely dependent on family history, women who are 25 years and older with history of thoracic radiation, strong family history or genetic predisposition (i.e. BRCA mutation or first degree relative of BRCA carrier), and women with Lobular Carcinoma in Situ (LCIS). CBE every 6 to 12 months, breast awareness and risk reduction strategies should be considered in the majority of women with increased risk of breast cancer as defined earlier.

The general principles for performing genetic counselling include: (1) there is a personal or family history suggesting genetic cancer susceptibility (2) the test can be adequately interpreted and (3) the results will aid in the diagnosis or influence the medical or surgical management of the patient or family members at hereditary risk of cancer. (Robson, et al., 2010).

Treatment of early breast cancer has evolved significantly over the past two decades. In the following section, we will introduce you to adjuvant (postoperative) systemic therapy for early breast cancer. The main goal of adjuvant therapy is to reduce recurrence rate, control any potentially remaining cancer deposits and improve survival.

3. Adjuvant therapy of early breast cancer

Breast cancer is considered early when the disease is detected in the breast only or in the breast and its locoregional lymph nodes and all the detected disease can be removed surgically (also called operable breast cancer). Surgical management of early breast cancer is beyond the scope of this chapter. Surgical resection is performed for local control and it removes the majority of the macroscopic disease but it doesn't eradicate local and distant microscopic components. This microscopic disease places the patient at high riskof local and systemic relapse. The goal of adjuvant therapy for early breast cancer is to eradicate any hypothetical occult local or distant disease, hence reduce the risk of recurrence and improve overall survival. Adjuvant systemic treatments for early breast cancer include chemotherapy, endocrine manipulation (endocrine therapy and ovarian ablation or suppression) in hormone receptor-positive tumors, and anti HER2 agents, (e.g. trastuzumab) for *HER2*-positive tumors. ER-positive early breast cancer is usually treated with the combination of chemotherapy followed by endocrine therapy (e.g. tamoxifen, or Aromastase Inhibitors - AIs) in post-menopausal women (*www.nccn.org,* 2010; Albian, et al., 2009). Endocrine therapy alone may represent an appropriate treatment for a group of patients who do not have high-risk breast cancer or are unlikely to benefit from chemotherapy.

Clusters of gene expression analysis may offer a better insight into breast cancer subtypes and their phenotypic behavior as well as response to therapy (Perou et al., 2000; Sorlie et al., 2001). Commercially available genomic assays like MammaPrint, Oncotype Dx, Theros, Map Qaunt Dx, and Mammostrat are increasingly used for the prediction of clinical outcome in patients with breast cancer (Sotiriou & Pusztai, 2009). Although commercially available, these assays have not been tested prospectively yet. These assays use a scoring system to classify patients as low, intermediate or high risk for disease

recurrence using a number of different targets to identify prognosis or predict efficacy of adjuvant therapy. Several studies are exploring prospectively the power of these assays (e.g. the TAILORx trial-Trial Assigning Individualized Options for Treatment (Rx), or MINDACT trials). Until the results become available and if successful, our approach for breast cancer treatment remains broad on the basis of expected effects of different interventions in broad categories of patients.

We are witnessing a paradigm shift that will adopt a patient-tailored approach and individualized therapy for early breast cancer based on the specific tumor genetic signature of the particular cancer.

3.1 Adjuvant endocrine therapy

Adjuvant endocrine therapy is recommended for almost all patients whose breast cancers have any detectable estrogen receptors (Goldhirsch et al., 2009). Endocrine therapy includes the use of Selective Estrogen Receptor Modulators (SERMs) and AIs. Optimal endocrine therapy in premenopausal women with early breast cancer remains an area of controversy although tamoxifen has been adopted as a standard therapy for decades and incorporated in treatment guidelines. The benefit of adding ovarian ablation (surgically or chemically with LHRH agonists) to tamoxifen therapy remains an area of investigation. A recent meta-analysis of retrospective data indicates that each of the possible endocrine interventions has an equal role and combinations do not improve long-term outcomes. TEXT, SOFT and PERCHE trials will hopefully shed some additional light and give the treating oncologist more guidance which therapy to chose. Even the duration of tamoxifen use remains somewhat arbitrary. Studies indicate that using tamoxifen beyond 5 years might actually reduce recurrences but some of the long-term side effects might outweigh the benefits.

For *postmenopausal* women, third-generation aromatase inhibitors are the accepted standard to all women with ER-positive cancers. For patients already on tamoxifen, switching to an aromatase inhibitor after 2 or 3 years should be considered in patients who did not experience a recurrent disease (Goldhirsch et al., 2009). There is substantial evidence to suggest that sequential chemoendocrine combination would approximately halve the average annual death rate from breast cancer during the first 15 years after diagnosis. (Early Breast Cancer Trialists Collaborative Group, 1998, 2005). The percentage of hormone receptor positive cells is a strong predictor of response to endocrine therapy both in the adjuvant and the metastatic settings (Regan et al., 2006). About 60% of breast cancers arising in premenopausal women and 80 % of those arising in postmenopausal women are ER or Progesterone receptor positive. Adjuvant endocrine therapy alone is usually advocated for breast cancers that are ER/PR positive, ≤ 2 cm, has minimal peritumoral vascular invasion, Ki-67 ≤ 15% (low proliferation index), node negative, grade I histology, and low multigene assay score (Goldhirsch et al., 2009; Montemurro & Aglietta, 2009). In the following section, we will describe the available hormonal therapies that are approved in the treatment of ER-positive breast cancer.

3.1.1 Tamoxifen

Tamoxifen is (Z)-2-[4-(1,2-diphenylbut- 1-enyl) phenoxy]-N, N- dimethylethanamine that is one of the selective estrogen receptor modulators (SERMs) and act as both an antagonist and a partial agonist of the estrogen receptor (Furr & Jordan, 1984). Adjuvant Tamoxifen therapy

for 5 years in women with ER positive breast cancer significantly reduces the annual recurrence, as well as breast cancer mortality in early breast cancer during the period of Tamoxifen use. (Early Breast Cancer Trialists Collaborative Group, 1998). The reduced risk of recurrence that is noticed with Tamoxifen use is solely dependent on the ER and not the PR status. (Early Breast Cancer Trialists Collaborative Group, 2005). The evidence suggests a protective carryover effect in reducing the risk of recurrence over the next few years and up to 15 years from starting Tamoxifen. Risk reduction after 5 years of Tamoxifen therapy is similar for younger and older women; however it is significantly greater for those with node positive disease in comparison to women with node-negative disease. (Early Breast Cancer Trialists Collaborative Group, 1998). The risk of thromboembolic disease and uterine cancer in women who took tamoxifen for 5 years is 0.2% per decade and is considered small in comparison to the absolute 10-year reductions in breast cancer mortality. On the other hand, tamoxifen may have a protective effect against heart disease. Tamoxifen resistance can potentially develop due to exaggerated agonist activity with potential impairment of its antitumor activity. Tamoxifen use for more than 5 years seems to be more effective than 5 years but at a price of much higher side effect profile and the standard recommendation remains for 5 years. (Early Breast Cancer Trialists Collaborative Group, 2005; Fisher et al., 1994)

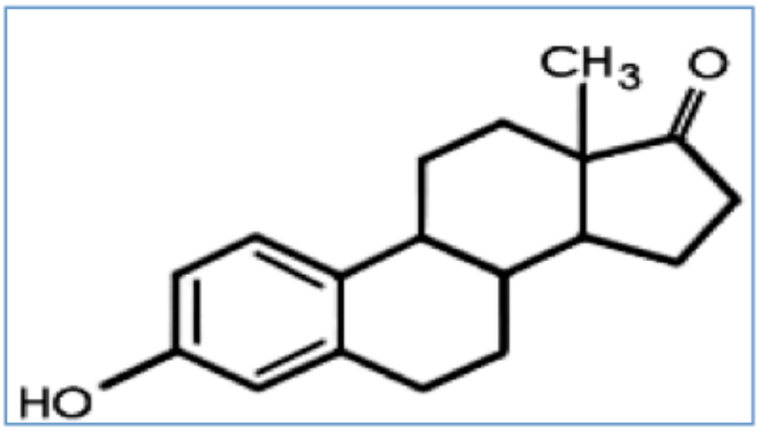

Fig. 1. Estrogen Chemical structure ($C_{18}H_{24}O_2$).

3.1.2 Aromatase inhibitors

In postmenopausal women, estrogen (C18H24O2) is produced in multiple extragonadal sites that include adipose tissues, osteoblasts, chondrocytes, vascular endothelium and smooth muscle cells, adrenal gland and numerous sites in the the brain. (Figures 1 and 2) Breast adipose tissue is not an exception for this synthesis and local production of Estrogen plays an important role in breast cancer microenvironment. These tissues usually produce Estrogen for their local use (as a paracrine or intracrine factor), which results in higher tissue concentration of Estrogen. This Estrogen can also escape metabolism and enter the circulation. Postmenopausal women have a higher level of circulating testosterone (C19H28O2) in comparison to Estradiol. (Simpson, 2003). Extragonadal tissues are dependent on external source of C_{19} androgenic precursors, since these tissues are incapable of converting cholesterol to the C_{19} steroid. Those C_{19} precursors provide a substrate for estrogen biosynthesis in these sites.

Aromatase is a cytochrome P450 enzyme that is involved in the conversion of C_{19} androgens to aromatic C_{18} estrogens *(figure 2.),* primarily in the ovary, and adrenal gland in females in addition to the testes in males (Santen et al., 2009; Simpson, 2003). Aromatase was recognized as a therapeutic target for the treatment of hormone-dependent breast cancer approximately 40 years ago (Santen et al., 2009). Compounds that inhibit aromatase decrease estrogen levels by affecting a key component of the production pathway, aromatase cytochrome P450. The aromatase cytochrome P450 enzyme is also active in peripheral tissues (fat, muscle, liver, and both epithelial and stromal breast cells).

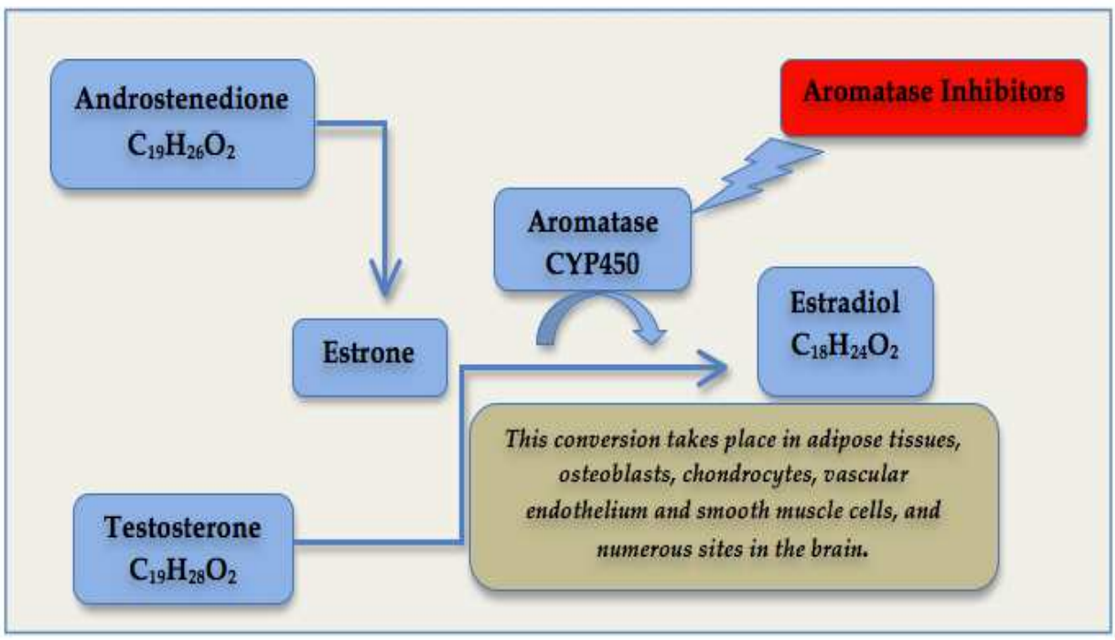

Fig. 2. Mechanism of action of Aromatase Inhibitors.

AIs are the standard of endocrine therapy for postmenopausal women with receptor-positive early, and metastatic Breast Cancer. AIs alone are contraindicated in premenopausal patients because if used alone, they do not suppress estrogen production adequately in women who are still ovulating possibly because of the interruption of the estradiol negative feedback and subsequent rise in luteinizing and follicle-stimulating hormones (Santen et al., 2009). In cases where tamoxifen is contraindicated, AIs may be administered to premenopausal women together with ovarian function suppression. In certain postmenopausal women, e.g. very low risk of recurrence, tamoxifen alone can be considered adequate.

Aminoglutethimide is considered the first generation of AIs. It is a non-selective inhibitor of adrenal steroidogenesis as well as thyroidal organification of iodine. Compared with the antiestrogen tamoxifen, aminoglutethimide had similar clinical efficacy but a higher incidence of adverse events; therefore, tamoxifen became the standard hormonal therapy for breast cancer (Harvey et al., 1982; Lipton et al., 1982; Smith et al., 1982).

More selective AIs that exhibit competitive, reversible, and/or mechanism-based inhibition were developed. The mechanism-based inhibitors produce a long lasting inhibition through their high specificty for the active enzyme site with less toxicity in comparison to with other

competitive inhibitors (Brueggemeier, 1994; Santen et al., 2009). Mechanism-based inhibitors include the steroidal AI, exemestane, and the nonsteroidal AIs, letrozole and anastrozole. Anastrozole and letrozole are reversible inhibitors, whereas exemestane is an irreversible inhibitor.

Several clinical trials evaluating adjuvant therapy in early breast cancer have demonstrated improved disease-free survival (DFS) in postmenopausal women with the use of anastrozole, exemestane, or letrozole in comparison to tamoxifen (Boccardo et al., 2005; Coombes et al., 2007; Cuzick et al., 2010; Goss et al, 2005; Jakez et al., 2005; Kaufmann et al., 2007; Mamounas et al., 2008).

AIs have been tested in the adjuvant settings in three different scenarios: initial treatment versus tamoxifen; sequential treatment after 2–3 years of tamoxifen to finish the duration of therapy for 5 years; and extended treatment after 5 years of tamoxifen. It is controversial, as of the best timing of AI use in the treatment program after surgery. Neither the optimal timing nor the duration of therapy is well established. Some studies suggest that ER+/PgR- negative patients respond better to upfront strategy of AI. For ER+/PgR+ positive tumors, there is more uncertainty, but initial use of an AI, for say 3 years, may still be better than sequencing it after 2 years of tamoxifen, as this is the period with highest recurrence rates. An upfront strategy may be favored over sequential or extended therapy. Generally speaking, AIs have a more tolerable side effect profile than tamoxifen, with lesser incidence of thromboembolic complications, fewer hot flashes and gynecologic symptoms, but more arthralgias, myalgias and have an increased risk of osteoporosis due to it primary effect in reducing estrogen levels. The combination of Tamoxifen and AIs is not additive and leads to more side effects (Cuzick et al., 2010).

3.2 Ovarian ablation or suppression

Ovarian ablation in premenopausal women is achieved by surgery or irradiation and ovarian suppression is accomplished by treatment with a luteinizing-hormone releasing-hormone agonists. There is evidence to suggest a definite effect of ovarian ablation or suppression both on recurrence and mortality from breast cancer in women < 50 years of age. (Early Breast Cancer Trialists Collaborative Group, 2005). Although tamoxifen plus ovarian function suppression is an accepted standard of endocrine therapies in premenopausal women (Goldhirsch et al., 2009), the addition of LHRH agonist to tamoxifen in this group of patients does not seem to decrease the probability of recurrence or death (Cuzick et al., 2007). In premenopausal women where tamoxifen is contraindicated, AIs with ovarian function suppression are now being tested in 3 randomized prospective clinical trials.

3.3 Chemotherapy

Defining the threshold for the use of cytotoxic chemotherapy is a difficult task: most RCT were performed in patients with early breast cancer who were selected on the basis of their pathological characteristics and anatomical staging, (e.g. large tumors or lymph node (LN) positive early breast cancer). The optimal duration or number of cycles to be given is not well established. Some of the factors used in decision making of chemotherapy use, include tumor size (pT > 5 cm), high histologic grade, high proliferation index (Ki-67 ≥ 10), vascular invasion, low expression of steroid hormone receptors, number of lymph nodes involved (≥ 4) and high multigene assay score. Ongoing research using genomic profiling assays (e.g.

Oncotype, MammaPrint, etc.) will add to the decision making process and identify patients who may or may not benefit from systemic cytotoxic therapy. Chemotherapy is the mainstay of adjuvant treatment of patients with triple-negative disease who are at sufficient risk of relapse to justify its utilization. Studies have showed a 33% risk reduction of recurrence as well as 26% risk reduction in mortality by using any kind of polychemotherapy in women aged 50 to 69 with ER-negative tumors. The respective reductions for patients with ER-positive tumors receiving tamoxifen were 15% for recurrence and 11% for mortality (Early Breast Cancer Trialists Collaborative Group, 2005). Patients with small primary tumors (pT1a pN0 and ER negative) might be spared adjuvant systemic therapy since the probability of recurrence is low and the potential benefit is negligible. In breast tumors that overexpress the HER-2 receptor protein (see section below), treatment with the monoclonal antibody trastuzumab, in addition to cytotoxic regimen provides incremental and significant benefits.

Identifying patients who would benefit from adjuvant chemotherapy in early breast cancer is a subject of debate. To optimize treatment of early breast cancer, it is important to understand the available chemotherapeutic agents and the advantage of choosing one over the other. There is a broad spectrum of chemotherapeutic agents available for the treatment of breast cancer and many regimens are nearly universal today. The first RCT by Bonadonna selected patients with LN positive early breast cancer after mastectomy and patients were randomized to receive chemotherapy or not. Cyclophosphamide is an alkylating agent that is used in combination with two antimetabolites, methotrexate and fluorouracil (CMF), in the treatment of early breast cancer. This combination was introduced into the management of early breast cancer in the mid-1970s and was the standard of care for some time (Bonadonna et al., 1976).

Over the last forty years, the addition of anthracyclines has been adopted as an integral part of most standard regimens. These agents inhibit tumor cell proliferation and gene expression by directly interacting with the DNA leading to the production of free radicals that destroy tumor cells. The most commonly used anthracyclines in breast cancer treatment are Doxorubicin and Epirubicin.

Adding doxorubicin to cyclophosphamide (AC combination) in the treatment of early breast cancer, proved to have equivalent efficacy to, as well as substantial advantages over, CMF in terms of tolerability, ease of administration and duration. Four cycles of AC was found to be equivalent to six cycles of CMF with respect to event-free survival, relapse-free survival (RFS), and overall survival (OS) in breast cancer patients regardless of nodal status, age, or estrogen-receptor (ER) status, but that AC offered the advantages of a shorter treatment course with fewer side effects (Fisher et al., 2001).

Cyclophosphamide, doxorubicin, fluorouracil (CAF) regimen have also shown similar efficacy in terms of OS when compare to CMF (Carpenter et al., 1994; Martin et al., 2003). In the subgroup of high-risk lymph node–negative patients, FAC use is associated with longer DFS and OS in comparison to CMF (Martin et al., 2003). Cyclophosphamide, Epirubicin, Fluorouracil (CEF) regimen has showed improvement in OS when compared to CMF. This benefit is true for women with node-positive disease (Levine et al., 2005; Bonneterre et al, 2005).

Anthracyclines remain important agents in adjuvant treatment and are indicated for adjuvant therapy regardless of the extent of nodal involvement, hormone receptor status, or HER-2 expression level. Anthracycline containing regimens are more effective at preventing

recurrence and increasing survival than CMF (Cyclophosphamide, Methotrexate and 5-FU) regimens (Early Breast Cancer Trialists Collaborative Group, 2005). This is true for the major subsets of early breast cancer patients including premenopausal (age <50) and postmenopausal (age, 50–69) patients, ER-poor and ER-positive patients, and both node-negative and node-positive patients. There is a positive correlation between delivery of the intended doses of chemotherapy on schedule and better treatment outcomes in breast cancer (Bonadonna et al., 1995; Budman et al., 1998). The optimal dose intensity in combination chemotherapy is a function of both the dose level and schedule. Minimizing the interval between cycles allows delivery of dose-dense chemotherapy (Glück, 2005).

It is believed that breast cancer growth follows Gompertzian kinetics and that shorter intervals between chemotherapy treatments allows dose-dense delivery and may result in a higher log-kill, thus leading to lower relapse rates and longer survival times (Citron et al., 2003; Norton, 1988). The use of growth factors (e.g., G-CSF) has enabled patients to tolerate dose dense chemotherapy by decreasing hematologic toxicities. Dose density and dose intensity are important part of the adjuvant treatment of early breast cancer, especially in women with node positive breast cancer.

Taxanes (docetaxel and paclitaxel) have added further survival benefit in the adjuvant treatment of early breast cancer regardless of hormone receptor status (Nowak et al., 2004; Martin et al., 2005; De Laurentiis et al., 2008). Studies comparing docetaxel, doxorubicin and cyclophosphamide (TAC) versus conventional fluorouracil, doxorubicin, and cyclophosphamide (FAC) in women with node–positive breast cancer showed a survival advantage favoring TAC (Martin et al., 2005, 2010). In addition, women with high-risk node negative disease, TAC was associated with improved rate of disease-free survival in comparison to FAC (Martin, 2010).

Sequential use of FEC followed by docetaxel (FEC-T) produced a significant DFS and OS in women 50-65 years of age with node-positive breast cancer. This regimen has become the standard of care in this age group and is considered a relatively well-tolerated regimen that contains anthracycline and taxane components. Women under the age of 50 years who received this combination did not gain a survival benefit (Roche et al., 2006).

Some studies have suggested that overexpression of HER-2 may correlate with greater sensitivity to anthracyclines. Thus the combination of trastuzumab (monoclonal antibody that inhibits signaling by HER-2 receptor) and an anthracycline-containing regimen for HER-2 positive breast cancer may confer an additional benefit in this disease subset (Paik et al., 2000; Muss et al., 1994).

Capecitabine has recently been tested in the adjuvant setting of early breast cancer. In women with medium- to high-risk early breast cancer, there was no difference in recurrence-free survival between docetaxel, capecitabine, cyclophosphamide, epirubicin (TX-CEX) versus docetaxel, cyclophosphamide, epirubicin, 5-fluorouracil (T-CEF); however, the addition of capecitabine may benefit a specific subgroup of patients with > 3 axillary metastases or triple-negative breast cancers. The use of TX-CEX was associated with higher discontinuation rate due to toxicity (Joensuu et al., 2010). Capecitabine is still being investigated and it has not become as part of the standard therapy of early breast cancer yet.

3.4 Targeted therapy with anti HER 2

Trastuzumab is a humanized hybrid monoclonal antibody that selectively binds to the extracellular domain of HER-2. Its anti tumor function is not well understood but it may

induce apoptosis, and also cause and antibody-dependent cell-mediated cytotoxicity. Trastuzumab has become an important component of breast cancer therapy regimens in metastatic as well as neoadjuvant settings of HER-2 expressing breast cancers (Salmon et al., 2001; Arteaga, 2003; Buzdar et al., 2005; Glück 2009; Dominici et al., 2010). Several large randomized clinical trials of high-risk patients with HER-2–positive early breast cancer have demonstrated that trastuzumab provides additional beneficial effects when used subsequent to anthracycline based chemotherapy and a taxane. One study also identified a non-anthracycline combination that seems to be equally effective without the cardio toxicity that is associated with anthracyclines plus trastuzumab. Several clinical trials have suggested that the addition of trastuzumab to standard chemotherapy may reduce the recurrence rate by approximately 50%. The standard duration of trastuzumab therapy is 1 year, although ongoing clinical trials are testing a shorter and longer duration of therapy.

Several large randomized clinical trials of high-risk patients with HER-2–positive early breast cancer have demonstrated that trastuzumab provides additional beneficial effects when used subsequent to anthracycline- based chemotherapy and a taxane. The National Surgical Adjuvant Breast and Bowel Project protocol B-31 (NSABP-B31) and the North Central Cancer Treatment Group (NCCTG) N9831 adjuvant trials were designed to compare doxorubicin-based chemotherapy followed by paclitaxel (AC→T) with AC→ T plus trastuzumab either in sequence or concurrent with paclitaxel. Preliminary efficacy findings from a combined analysis of those trials after a median follow-up of 2.9 years showed more than 50% relative reduction in the risk for recurrence, with significant reductions in risk both in terms of DFS and OS with AC→T plus trastuzumab compared with AC→T (Perez et al., 2007). Doxorubicin-based chemotherapy (AC) followed by paclitaxel plus trastuzumab either in sequence or concurrent with paclitaxel reduces the risk of breast recurrence by half in addition to significant improvement in DFS and OS (Romond et al., 2005).

The trastuzumab Adjuvant (HERA) trial randomly assigned patients with HER-2–positive invasive breast cancer to receive either trastuzumab for 1 or 2 years or observation, with a primary end point of DFS; patients were previously treated with surgery and adjuvant or neoadjuvant chemotherapy (Martine et al, 2005). Unlike the NSABP-B31 and N9831 trials, most patients in the HERA trial did not receive a taxane, and about 30% of patients were node-negative. Median follow-up at 2 year after randomization demonstrated a significant improvement in disease-free survival (DFS) and overall survival (OS) in trastuzumab-treated patients, compared with observation (Smith, I et al., 2007).

The breast cancer international research group trial (BCIRG006) compared AC→T (Docetaxel) with AC→TH (Docetaxel, Trastuzumab) and with TCH (Docetaxel, Carboplatin, Herceptin) in the adjuvant treatment of HER2-amplified early breast cancer. Trastuzumab was found to provide a similar and significant advantage for both DFS and OS when used with either anthracycline-based (AC → TH) or non-anthracycline (TCH) chemotherapy in both high and low-risk patients. TCH seems to have a better side effect profile in comparison of AC→TH (Robert et al., 2007)

The FINHER trial was originally designed to compare treatment-using docetaxel versus vinorelbine in early breast cancer. The patients were randomized to three cycles of docetaxel or vinorelbine followed by three cycles of fluorouracil, epirubicin, and cyclophosphamide. The subset of patients with HER-2-positive cancers was further randomized to either receive or not receive trastuzumab for 9 weeks together with the first three cycles of docetaxel or vinorelbine. Within this subgroup, DFS was significantly better among those who received trastuzumab and there was a trend toward better OS (Joensuu et al., 2006).

The findings of the NSABP-B31, NCCTG-N9831, HERA, BCIRG006 and FINHER trials have established that the addition of trastuzumab to anthracycline-based chemotherapy, either with or without a taxane, may reduce the recurrence rate by approximately 50%. Trastuzumab has become the standard backbone to chemotherapy in treating patients who have HER-2–overexpressing breast cancers.
New compounds that target HER2 are in development; Lapatinib is a dual erbB 1 and 2 tyrosine kinase inhibitor that blocks HER-2 receptor and has an antiproliferative effect. Lapatinib has been approved by the FDA for the use in metastatic breast cancer; these compounds are now under clinical investigation in early breast cancer. Dual HER2 blockade using trastuzumab and lapatinib to overcome resistance is a concept under investigation for treatment of HER2-positive early breast cancer (Abramson & Arteaga, 2011). No data are available in the adjuvant setting at present time. A recent clinical trial in women with HER2-positive primary breast cancer, neoadjuvant lapatinib plus trastuzumab given with paclitaxel was associated with a significant improvement in pathologic CR (pCR) rate versus trastuzumab or lapatinib with paclitaxel alone (Baselga et al., 2010).

3.5 Radiation therapy

Sequencing of radiotherapy in relation to chemotherapy in early breast cancer is a subject of debate and investigation. Synchronous (using CMF based chemotherapy) versus sequential chemotherapy and radiotherapy is feasible but has no advantage in reducing the risk of locoregional recurrence but it shortens the duration of adjuvant therapy.

4. Summary and conclusion

Breast cancer is the most common diagnosed malignancy in the western world and increasingly in the developing countries;. Early or operable breast cancer is a disease that involves the breast only or the breast and its locoregional lymph nodes. Histo-pathological diagnosis, Estrogen, Progesterone and HER-2 receptor status are important markers for prognosis and decision making in choosing the appropriate adjuvant therapy after successful surgical removal of the primary cancer. Modern molecular assays are utilizing the fact that breast cancer is a genetic and heterogeneous disease: these tests have the potential to not only better give the prognosis but also be used as predictive tests to identify effective therapeutic regimen and spare the patient unnecessary and potentially toxic treatment. As standard of practice, estrogen receptor positive cancers should be treated with hormonal therapy; the use of chemotherapy is driven by the risk of recurrence and must be carefully brought into context with its toxicity. HER-2 positive cancers are high-risk cancers regardless of size or ER status and should almost always be treated with trastuzumab in addition to chemotherapy. Anthracyclines and Taxanes containing cytotoxic combinations, as integral components of most regimens, are accepted treatment standards.
Adjuvant systemic therapy has changed the outcome of early breast cancer substantially over the last decades. Newer compounds and better understanding of the available hormonal, targeted and chemotherapeutic agents will further improve our success in treating early breast cancers.

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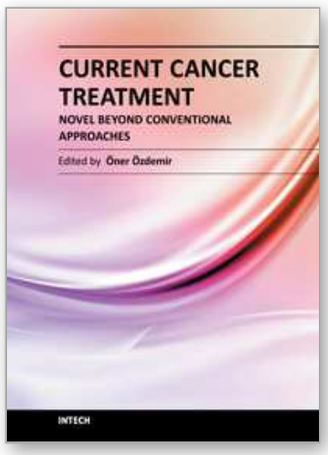

Current Cancer Treatment - Novel Beyond Conventional Approaches

Edited by Prof. Oner Ozdemir

ISBN 978-953-307-397-2
Hard cover, 810 pages
Publisher InTech
Published online 09, December, 2011
Published in print edition December, 2011

Currently there have been many armamentaria to be used in cancer treatment. This indeed indicates that the final treatment has not yet been found. It seems this will take a long period of time to achieve. Thus, cancer treatment in general still seems to need new and more effective approaches. The book "Current Cancer Treatment - Novel Beyond Conventional Approaches", consisting of 33 chapters, will help get us physicians as well as patients enlightened with new research and developments in this area. This book is a valuable contribution to this area mentioning various modalities in cancer treatment such as some rare classic treatment approaches: treatment of metastatic liver disease of colorectal origin, radiation treatment of skull and spine chordoma, changing the face of adjuvant therapy for early breast cancer; new therapeutic approaches of old techniques: laser-driven radiation therapy, laser photo-chemotherapy, new approaches targeting androgen receptor and many more emerging techniques.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Muaiad Kittaneh and Stefan Glück (2011). Adjuvant Therapy for Early Breast Cancer, Current Cancer Treatment - Novel Beyond Conventional Approaches, Prof. Oner Ozdemir (Ed.), ISBN: 978-953-307-397-2, InTech, Available from: http://www.intechopen.com/books/current-cancer-treatment-novel-beyond-conventional-approaches/adjuvant-therapy-for-early-breast-cancer

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