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Short Communication

Breast Cancer Agents: Treatment & Prevention

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INTRODUCTION

The heterogeneous disease Breast Cancer (BC) is an ancient disease which was noted 3500 years ago by ancient Egyptians [1] .The heterogeneity, including intratumor heterogeneity and intertumor heterogeneity, is influenced by genetic and non-genetic factors. Furthermore, BC is the most common malignant tumor and the second leading cause of cancer death in women. Because BC is a heterogeneous disease, no single therapy is sufficient to treat all patients. In order to assess prognosis and determine the appropriate therapies for BC patients, many criteria like patient age, axillary lymph node status, tumor size, histological grade and lymphovascular invasion, hormone receptor status, and HER2 status have been used to categorize the disease. Based on recent molecular techniques, particularly gene expression profiling and immuno- histology, BC can be classified into four major types: estrogen and progesterone receptor positive luminal A and luminal B, HER2 and basal-like/ triple negative BC [2]. If BC is diagnosed early, women have better prospects for survival. However, most women diagnosed with this disease will undergo systemic or local therapies to treat the disease. The therapies involve

Surgeons, radiation oncologists, medical oncologists and others working together to provide treatment. Surgery is the first line treatment. However, a variety of other medical therapies have also been used: radiotherapy, chemotherapy, hormonal therapy, bisphosphonate therapy and targeted biological therapy and others [3-12].

Table 1 summarizes the agents which are approved by the USFDA to treat BC. There are four major common classes of agents for BC treatment: chemotherapy agents, hormonal therapy agents, bisphosphonate therapy agents, and targeted biological agents.

(https://www.breastcancertrials.org/BCTIncludes/Resources/BreastCancerDrugs.html)

Chemotherapy agents consist of systemic drug treatments intended to stop cancer cells dividing and growing [13-15]. There are 6 types of chemotherapeutic agents: alkylating agents, anthracyclines, platinum agents, taxanes, vinca agents, and other chemotherapeutic agents. Alkylating agents work by inserting an "alkyl group (C_nH_{2n+1})" into the DNA structure to interfere with DNA replication and prevent cancer cells from dividing. The alkyl group is attached to the number 7 nitrogen atom of the purine ring of the guanine base of DNA. In general, cancer cells are proliferating faster with less active DNA error-correcting repair than healthy cells; therefore cancer cells are more sensitive to DNA damage. Anthracyclines, antibiotics derived from the bacterium *Streptomyces peucetius var. caesius,* attack cancer cells largely by disrupting DNA structure and preventing cell division. The anthracyclines are among the most effective anticancer agents ever developed and are effective against many types of cancer. However, they cause significant cardiotoxicity and neurotoxicity. Platinum agents, anti-cancer drugs that contain the metal platinum, cause crosslinking of DNA as monoadduct, interstrand crosslinks, intrastrand crosslinks, or DNA protein crosslinks, all of which block DNA repair and/or DNA synthesis in cancer cells. These agents sometimes also included among alkylating agents because they have similar mechanisms as anti-cancer agents. Taxanes, mitotic inhibitors, act by interfering and disrupting the cellular microtubules. The microtubules play an important role in many cellular functions, including cell division. Taxanes are often used in combination with other chemotherapy agents. Vinca alkaloid agents, originally derived from the Periwinkle plant *Catharanthus roseus,* are a set of anti-mitotic and anti-microtubule agents. They are cell- cycle-specific cytotoxic drugs that inhibit the ability of cancer cells to divide by preventing the polymerization of tubulin into microtubules. There are also some chemicals agents that can be used to treat breast cancer, which do not belong to the aforementioned groups: Fluorouracil (5-FU), Irinotecan, Gemcitabine, Eribulin, Ixabepilone, Methotrexate, Temozolomide, Topotecan, Vincristine, Vinblastine, and Capecitabine. Collectively, all of these chemotherapeutic agents are often associated with unpleasant side effects because, in addition to cancer cells, they target all rapidly growing cells, including those in the gastrointestinal tract, bone marrow, testicles and ovaries [16,17].

BC is a hormonally dependent disease in, at least, a proportion of patients [1,18]. Hormonal therapy agents, through manipulation of the endocrine system, inhibit production

Table 1: FDA approved agents for management of BC.

Classes	Sub-classes	Name of agents	Mechanism of Action
Chemotherapy Agents	Alkylating Agents	Cytoxan® / Cyclophosphamide Thiotepa	Inserts an alkyl moiety into the DNA structure, which blocks cell division
	Anthracyclines	Adriamycin® / Doxorubicin Doxil® / Liposomal Doxorubicin Ellence® / Epirubicin Novantrone® / Mitoxantrone	Disrupts duplex DNA structure, which blocks cell division
	Platinum Drugs	Paraplatin® / Carboplatin Platinol® / Cisplatin	DNA crosslinking that inhibits DNA repair mechanisms, leading to cell death
	Taxanes	Abraxane® / Paclitaxel Protein-bound Taxol® / Paclitaxel Taxotere® / Docetaxel	Disrupts cellular microtubules to inhibit cell growth and stopcell division
	Vinca Agents	Navelbine® / Vinorelbine	Disrupts cellular microtubules to inhibit cell growth and stop cell division
	Other Chemotherapy Agents	Adrucil® / Fluorouracil (5- FU) Camptosor® / Irinotecan Gemzar® / Gemcitabine	
		Halaven® / Eribulin	
		Ixempra® / Ixabepilone Methotrexate	
		Temodar® / Temozolomide	
		Topotecan	
		Vincristine	
		Vinblastine	
		Xeloda® / Capecitabine	
Hormonal	Anti-Estrogen	Evista® / Raloxifene	Binds to estrogen receptors
Therapy	Agents	Fareston® / Toremifine	to block estrogen activity
Agents		Faslodex® / Fulvestrant	and its associated growth-
		Nolvadex® / Tamoxifen	promoting activities
	Aromatase	Arimidex / Anastrozole	Inhibits aromatase to block
	Inhibitors	Aromasin / Exemestane	estrogen production
		Femara / Letrozole	
	Ovarian	Lupron® / Leuprolide	Reduces the ovarian
	Suppression	Plenaxis® / Abarelix	capacity to produce estrogen
		Suprefact® / Buserlin	
		Zoladex® / Goserelin	
	Other	Megace® / Megestrol Acetate	
	Endocrine/Hor		
	mone agents		
Bisphosphon	Bisphosphonate	Actonel® / Risedronate	Inhibits breast cancer bone
ate Therapy	agents	Aredia® / Pamidronate	metastasis
Agent		Boniva® / Ibandronate	
		Fosamex® /Alendronate	
		Xgeva® /Denosumab	
		Zometa® / Zoledronate	
Targeted	Targeted	Afinitor® / Everolimus	Inhibits the mammalian
Biological	mTOR		enzyme target of rapamycin
Agents			(mTOR)
	Targeted	Avastin® / Bevacizumab	Suppresses tumor growth by

	Angiogenesis		blocking angiogenesis to
			reduce the blood supply to
			tumors
	Targeted Her2	Herceptin® / Trastuzumab	Monoclonal antibody; Inhibits cell division by
			blocking growth factors
			binding to Her2 receptor
		Kadcyla® / T-DM1 (Ado-	A combination of Herceptin
		trastuzumab emtansine)	and a chemotherapy drug
			(DM1) to inhibit cell growth
		Lapatinib® / Tykerb	Blocks the HER2/neu

or activity of hormones (hormone antagonists), largely 17 β-estradiol, that promote tumor growth. These agents include anti-estrogen agents, aromatase inhibitors, ovarian suppression, and other Endocrine/Hormone agents. For patients with luminal A/B breast cancer, hormone-receptor positive (ER, PR-positive), hormone therapy with anti-estrogen agents (Raloxifene, Toremifine and Fulvestrant) and aromatase inhibitors (anastrozole, letrozole, exemestane) or ovarian suppression (in premenopausal patients) are the common strategies to treat this disease, often combined with other therapies [18].

Bisphosphonate therapy agents, commonly used for osteoporosis, have been approved by FDA to treat Metastatic Breast Cancer (MBC) which has spread to the bones [19,20]. Bisphosphonate therapy agents may also be used in combinations with aromatase inhibitors for early stage breast cancer to lessen the adverse effect of aromatase inhibitors to weaken bone in some patients. This sub-class of agents includes risedronate, pamidronate, ibandronate, alendronate, denosumab and zoledronate.

Targeted biological agents can selectively inhibit various mechanisms, include autocrine growth signals, continuous replicative potential, angiogenesis, and stromal invasion with the development of metastases. mTOR, angiogenesis and HER2 are among the targets for which these agents have been developed. HER2 positive breast cancer accounts for 20–25% of all breast cancer patients, and HER2 over expression deregulates activation of intracellular mitogenic signaling and leads to aggressive tumor behavior. The first drug to target HER2, Trastuzumab, is a recombinant humanized monoclonal antibody which binds to HER-2/neu protein to interfere with ligand binding and subsequent activation of the HER2 signaling pathway. Other FDA approved agents in this category include T-DM1, Tykerb and Pertuzuma, which work in different ways to block the HER2 pathway [21-23]. The vascular endothelial growth factor (VEGF) receptor family plays an essential role in angiogenesis that supports tumor growth. Therefore, targeting the VEGF pathway is another way to treat BC [24,25]. The FDA approved agent Bevacizumab is a monoclonal anti-body that can block angiogenesis in cancer. The mammalian target of rapamycin, mTOR, a human protein encoded by the *MTOR* gene, is a serine/threonine protein kinase that regulates cell growth, cell proliferation, cell motility, cell survival, protein synthesis and transcription. mTOR is a member of the phosphatidylinositol 3-kinase-related kinase protein family. The inhibitor everolimus interferes with cancer cell growth by blocking the mTOR pathway [26,27]. Resistance to anti-HER2 agents is a problem for targeted HER2 therapy. The resistance may be because of aberrant activation of signaling pathways downstream of the receptor, such as the presence of activating *PI3K* mutations or loss of function of the phosphatase PTEN or increase Rac1 activation. In our study we have found that inhibition of both Akt and Rac1 pathways resulted in a significantly more decrease of Trastuzumab resistance than inactivation of Rac1 or Akt alone [28]. Combination therapies are under investigation to overcome the resistance problem. In a recent Phase Ib study, paclitaxel, mTOR inhibitor everolimus and trastuzumab were combined together to treat the patients with HER2-overexpressing metastatic breast cancer pretreated with trastuzumab [29].

Basel like/Triple negative breast cancer, defined as tumors that are negative for Estrogen Receptor (ER), progesterone receptor (PR), and HER2, is a biologically aggressive disease with limited treatment options, in part due to the lack of these receptor targets. Chemotherapy is one treatment option [30].

Chemoprevention has been defined by Sporn as "the use of pharmacologic or natural agents that inhibit the development of invasive breast cancer either by blocking the DNA damage that initiates carcinogenesis, or by arresting or reversing the progression of premalignant cells in which such damage has already occurred" [31]. Selective Estrogen Receptor Modulators (SERMs) and Aromatase Inhibitors (AIs) have been investigated as BC chemoprevention agents. While they are effective in prevention of endocrine responsive lesions, they have no effect in reducing the risk of estrogen receptor-negative BC. Tamoxifen and raloxifene are two effective agents used for the prevention of breast cancer in women at high risk for the development of the disease. Raloxifene has more side effects than tamoxifen. New agents are still under investigation for BC prevention [31-33].

Even though progress has been made in BC diagnosis and treatment, BC is still a major health problem for women. The identification of new potential molecular targets and development of new agents to target these molecules in BC will have a significant impact on future BC therapy and provide a wealth of opportunities for chemoprevention also. There are many new targets currently being investigated, including the programmed death-1 (PD-1) pathway [34], protein phosphatase 2A(PP2A) [35], the BCL-2 pathway [36], cell cycle machinery [37], the quiescin sulfhydryl oxidase 1 (QSOX1) pathway [38],

microRNA pathways [39] and some others [40-42].

Also many novel delivery systems are currently being investigated: nano-particles, polymeric micelles, nano-micellar carriers, and others [43-45]. Even though the full mechanisms of action have not yet been elucidated, traditional Chinese herbal medicines have been used in disease prevention and treatment for centuries [46,47]. These agents may present alternative strategies to western cancer therapies. In addition, life styles decisions are likely also important factors for BC development, prevention and treatment. In a recent study in mice, we found that high fat diet initiated in puberty increases the breast cancer risk in adulthood [48].Other factors, including alcohol, tobacco, and cosmetics may also influence BC risk [47,49-52].

CONCLUSION

The progress in breast cancer management requires multidisciplinary team efforts which involve basic researchers, radiologists, pathologists, surgeons, radiation oncologists, medical oncologists and psychologists. The development of rational, effective, and safe agents for prevention or treatment, involving targets in multiple regulatory pathways and with the ability to modify carcinogenesis in its early phases, will be desirable.

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