

Breast Cancer: A Review on Molecules, Herbal Medicines, Tumor Markers and Current Clinical Trial Status

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Abstract: Cancer is a well-known challenge to the human kind ever since the existence of Medical knowledge. From the age of 1600 B.C. when it was first discovered and described by “Edwin Smith” and “George Ebers” papyri, later described by Hippocrates as *Carcinos*, till today; Cancer has spread at an alarming rate and possess test for Medical and Clinical research world. In general terms cancer or *carcinosis* is term defined in medical science for any kind of uncontrolled growth of cells which spreads from the region of occurrence to the other parts of the body like poison. Study of cancer is termed as an Oncology. Recent research and study have found various reasons for causing cancer and are termed as carcinogens or cancer causing agents. Cancer research have found various carcinogens responsible for triggering the initiation of cancer in the body and One such research study believes the inheritance of cancer among genes. Approximately there must be faults in 6 or more than 6 genes in the cells to turn them into cancerous. Breast cancer is termed as cancer of cells in Breast region and exists today as widest of all cancers among 140 out of 184 countries. Globally the occurrence rate of Breast cancer is 1 out of 4 cancers. This highlights the huge market for pharmaceutical and clinical research industry. The present review thus highlights the facts and figures of the commonest of all cancers, the breast cancer, the treatment options available with us in molecular terms and the cure which lies in traditional medicines. The review also highlights the current market size and future and the latest clinical trials happening across globe. With the advancing technologies and sources of treatments available with us, the time is no far when we can find specific cure for different types of cancer, especially the breast cancer.

INTRODUCTION

Cancer pronounced as /'kansə/ is one of the dreaded disease faced by humans from the age it has come into an existence. It is described as an irregularity in the cell functions which result into the development of abnormal cells which form abnormal Organ growth and causes discomfort to the body, followed by, death.

As depicted in Figure 1 during cell cycle growth and generation, when the damaged DNA gets transformed into damaged cell and instead of apoptosis (programmed cell death), it starts forming colonies of its like cells and it becomes a mass of mutated cells, which is termed as Cancer. ^[1] The history of Cancer dates back to 1600 BC described first in Egyptian manuscripts and was described in texts of Edwin smith papyrus. ^[2] The term cancer was first described by Hippocrates (460-370 BC) as *carcinosis* the Greek physician to describe an ulcer forming and non-ulcer forming tumors. The roman physician Celsus (28-50 BC) then later transformed the Greek term *carcinosis* to Cancer, which we use nowadays and describe the disease with. The study of cancer is known as Oncology and the medical practitioners who are involved in the practice of Oncology are termed as Oncologist. The term *Onco* was coined by another Greek physician known as Galen (130-200 AD). There are many theories associated with the Cancer to describe it by the people earlier associated with its study and practice. These theories are mainly, a) Humoral Theory: The Humoral theory believed in im-balance between the humors which existed in the human body. Hippocrates believed that Human body consists of 4 humors or fluids i.e. blood, phlegm, yellow bile and black bile. Imbalance in these fluids resulted in disease as believed earlier. The existence of black bile in all organs

was believed to be the cause of cancer or *carcinosis* at the time of Middle age and existed for 1300 years. b) Lymph Theory: This theory believed the cause of cancer due to existence of another fluid known as lymph. The scientists and theorists in this age i.e. 1700's believed the reason of cancer due to fermentation and degeneration of lymph. c) Blastema Theory: The age of 1838 and few years, scientists believed the reason of cancer due to Blastema which is region between cells. It was clear in this age that Cancer was not from Normal cells, but from an abnormal mass or cells. German pathologist J. Muller believed in blastema to cause cancer. d) Trauma Theory: It was believed that cancer was caused due to certain kind of trauma or injury to the body, which is now stated as false after numerous experiments of causing injuries to animal body and not resulting into cancer and the last theory associated with the cancer is the e) Infectious Disease Theory: Two doctors simultaneously confirmed that Cancer is in all infectious. The credit goes to Zacutus Lusitani and Nicholas Tulp. This theory is still correct at present times as one of the reason of cancer has been found in the existence of virus known as Human papilloma virus, which causes around 90 % of Cervical cancer. ^[3]

CANCER CELL CYCLE

Cancer is often considered as a disease due to irregularity in cell cycle. Cell cycle is the series of functions which are involved in growth and development of cell.

As described in Figure 2, the cell cycle consists of G0 phase, G1 phase, S phase, G2 Phase and M phase. Cell cycle or normal cell cycle is important for growth, development, division and production of colonies for the normal wellbeing of the organelles, the organ and the human body. G0 phase is the resting phase where neither the growth nor division of cell takes place, G1 phase the cell grows in size and preparation of DNA takes place, S phase is the phase where DNA replication starts taking place, G2 phase the cells continue to grow and prepares for division, M phase is

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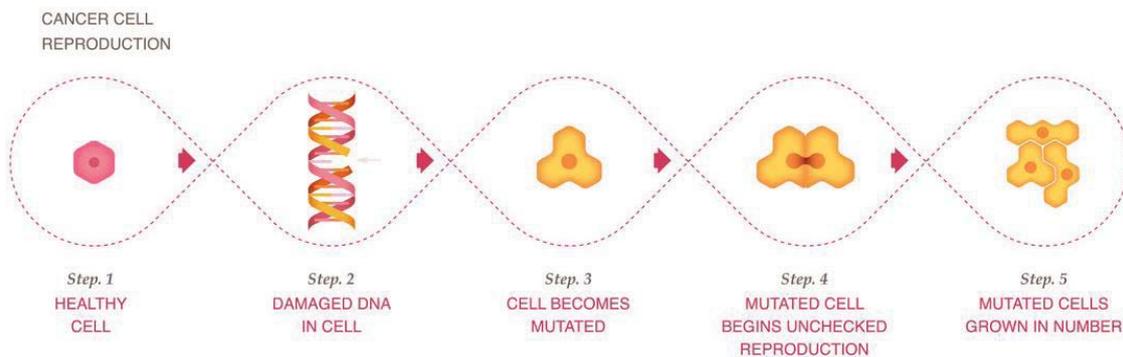


Figure 1: Cancer Cell growth [1]

Cell Cycle

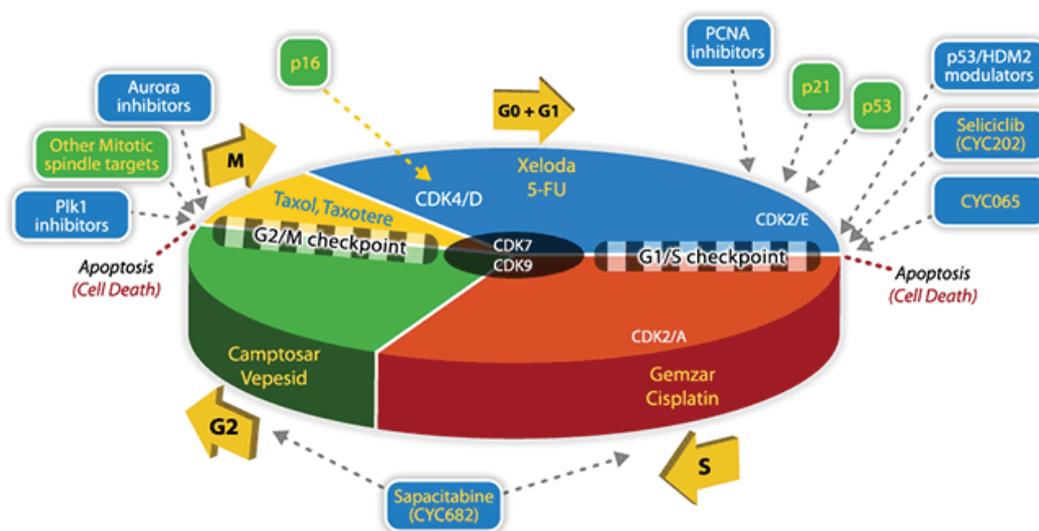


Figure 2: Cell cycle [4]

the phase where actual division takes place and cells produce two daughter cells, again the cells enter the G0 phase and thus cell cycle continues in the same manner and growth takes place. [4] As mentioned earlier that cell cycle is highly regulated process, the regulation depends upon the balance between the positive regulators and negative regulators. Cyclin-dependent kinases and their cyclin partners are the positive regulators and cyclin-dependent kinase inhibitors are the negative regulators. When imbalance between the positive regulators and negative regulators takes place, it results in production of damaged cells and thus cancer starts originating due to tumor generation. It is frequently associated with mutations or abnormalities in the positive and negative regulators i.e. cyclins thus is the basis of Cancer generation. Thus this is the general theory which lies in the heart of Cancer generation and its progress. [5]

Cancer is associated with one of the biggest disease having high degree of morbidity and mortality. It is estimated that the number of new cases of cancer would reach to 24 million per year by the end of 2035 world over. It is estimated that by 2030 around 13 million deaths will be associated with the cancer. [6]

Cancer therapy is highly advanced nowadays. There are many cancer therapies available with us to deal with Cancer. Anti-cancer modalities have advanced to greater extent in the past fifteen years. The major site of action of cancer therapies includes creating damage to the DNA of abnormal or tumor cells. The treatment modalities includes targeting, 1.) Growth factor receptors, 2.) Intracellular signaling pathways, 3.) Epigenetic processes, 4.) Tumor vascularity, 5.) DNA repair defects and 6.) Cell death pathways. [7]

CLASSIFICATION OF ANTI-CANCER DRUGS

The classification of Anti-cancerdrugs include, 1) Alkylating agents, 2) Anti-metabolites, 3) Natural products, 4) Hormones and Antagonists, 5) Miscellaneous agents. The same has been described in Table 1. [7]

TYPES OF CANCER

Cancer is one of the vast forms of disease, every body part and type has cancer associated with it. Types of cancer are, Adrenal cancer, Anal cancer, Bile duct cancer, Bladder cancer, Bone cancer, Brain/ CNS cancer, Breast cancer, Breast cancer in Men, Castleman disease, Cervical cancer,

Table 1: Cancer Drugs [7]

Alkylating Agents		
Nitrogen Mustards	Mechlorethamine, Cyclophosphamide	Hodgkin disease
	Ifosfamide	Acute and chronic lymphocytic leukemia
	Melphalan	Multiple Myeloma
	Chlorambucil	Chronic lymphocytic leukemia
	Procarbazine	Hodgkin disease
Methylhydrazine derivatives	Busulfan	Chronic Myelogenous leukemia
Alkyl sulfonate	Carmustin, Streptozocin	Hodgkin disease, Malignant carcinoid,
Nitrosoureas	Bendamustine	Non-Hodgkin lymphoma
Triazines	Dacarbazine, Temozolomide	Malignant gliomas
Platinum coordination complexes	Cisplatin, carboplatin, oxaliplatin	Testicular, Ovarian, bladder, esophageal, lung, breast cancer
Antimetabolites		
Folic acid Analogs	Methotrexate, Pemetrexed	Acute Lymphocytic leukemia, breast cancer
Pyrimidine Analogs	Fluorouracil, Cytarabine, Gemcitabine	Breast, colon, stomach cancers
Purine Analogs and related Inhibitors	Mercaptopurine, Pentostatin, Fludarabine, clofarabine	Small cell Non-hodgkin lymphoma, Chronic Lymphocytic leukemia
Natural Products		
Vinca Alkaloids	Vinblastin, Vinorelbine, Vincristine	Testis cancer, Breast cancer, Lung cancer
Taxanes	Paclitaxel, Docetaxel	Ovarian, Breast cancer, Head and neck cancer
Epipodophyllotoxins	Etoposide, Teniposide	Testis, small cell lung cancer
Camptothecins	Topotecan, Irinotecan	Ovarian cancer, small cell lung cancer
Antibiotics	Dactinomycin, Daunorubicin, Doxorubicin	Chorior sarcoma, Wilm's tumor
Echinocandins	Yondelis	Soft-tissue sarcoma, ovarian cancer
Anthracenedione	Mitoxantrone, Bleomycin, Mitomycin C,	Breast and prostate cancer
Enzymes	L-Asparaginase	Acute lymphocytic leukemia
Hormones and Antagonists		
Adrenocortical suppressants	Mitotane	Adrenal cortex cancer
Adrenocortico-steroids	Prednisone	Acute and Chronic lymphocytic leukemia
Progestins	Hydroxyprogesterone caproate	Endometrial, Breast Cancer
Estrogen	Diethylstilbestrol, Ethinyl estradiol	Breast and Prostate cancer
Anti-estrogens	Tamoxifen, Toremifene	Breast Cancer
Aromatase Inhibitors	Anastrozole, Letrozole,	Breast Cancer
Androgens	Testosterone propionate	Breast Cancer
Anti-androgens	Flutamide, Casodex	Prostate Cancer
GnRH analog	Leuprolide	Prostate Cancer
Miscellaneous Agents		
Substituted urea	Hydroxyurea	Chronic Myelogenous leukemia
Differentiating agents	Tretinoin, Arsenic trioxide	Cutaneous T-cell lymphoma
Protein tyrosine kinase inhibitors	Histone deacetylase	GI Stromal tumors,
Proteasome inhibitors	Imatinib, Dasatinib, nilotinib, Gefitinib,	Breast cancer
Biological response modifiers	Lapatinib	Multiple myeloma
Immunomodulators	Bortezomib	Hairy cell leukemia, Kaposi's sarcoma, melanoma
mTOR Inhibitors	Interferon- alpha, interleukin	Multiple myeloma
monoclonal antibiotics	Thalidomide, Lenalidomide	Renal Cancer
	Temsirolimus, Everolimus	

Colon/Rectum cancer, Endometrial cancer, Esophagus cancer, Ewing family of tumors, Eye cancer, Gallbladder cancer, Gastrointestinal carcinoid tumors, Gastrointestinal stromal tumor, Gestational trophoblastic disease, Hodgkin disease, Kaposi sarcoma, Kidney cancer, Laryngeal and Hypopharyngeal cancer, Leukemia, Liver cancer, Lung cancer, Lung cancer- non small cell, Lung cancer- small cell, Lymphoma, Lymphoma of skin, Malignant Mesothelioma, Multiple myeloma, Myelodysplastic syndrome, Nasal cavity and Paranasal Sinus cancer, Nasopharyngeal cancer, Neuroblastoma, Non-Hodgkin Lymphoma, Oral cavity and Oropharyngeal cancer, Osteosarcoma, Ovarian Cancer, Pancreatic cancer, Penile cancer, Pituitary tumors, Prostate

cancer, Retinoblastoma, Rhabdomyosarcoma, Salivary gland cancer, Sarcoma-Adult Soft Tissue cancer, Skin cancer, small intestine cancer, Stomach cancer, Testicular cancer, Thymus cancer, Thyroid cancer, Uterine Sarcoma, Vaginal cancer, Vulvar Cancer, Waldenstrommacroglobulinemia, Wilm's tumor. [9]

GLOBAL CANCER MARKET

It is estimated that Global Anti-cancer drugs market would reach \$ 111.9 billion by 2020. As many cancer drugs are going to face patent expiration, it will boost the Anti-cancer drug markets. The major drugs who are on the plunge of patent expiration are, Herceptin, Erbitux, Rituxan and

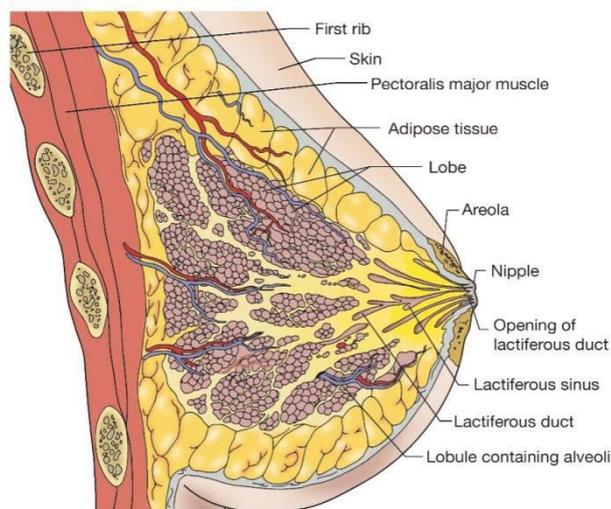


Figure 3: Normal breast anatomy [10]



Figure 4: Breast cancer [12]

Avastin. In the research and endeavor towards market growth, it is estimated that biological therapies would dominate the anti-cancer market by 2020.

Globally, North-America would dominate the market as it is in the present time, with around 38 % share in the overall oncology drug market. It is also estimated that Asia-Pacific market would grow at the promising CAGR of 8.7%. [8]

BREAST CANCER

Human Breast consists of branching ductal network which consists of two epithelial cell types, 1) Inner layer of polarized luminal epithelial cells and., 2) An outer layer of myoepithelial cells, separated from Collagenous stroma with the help of laminin rich basement membrane. The ductal network terminates in lobular units commonly referred to as the terminal duct lobular units (TDLUs). The TDLUs, composed of lobules that contain acini that function to secrete milk during lactation, are formed from tubular epithelial structures through a process called branching morphogenesis which is a highly conserved developmental process seen across the animal kingdom. This process gives rise to the airways of the lungs, the urine-collecting ducts, the prostate and salivary glands as well as the functional unit of the breast. [11] Thus female breast consists of three types of cells, mainly, Lobules (Milk producing glands), Ducts (Cells which carry milk from lobules to nipple) and Stroma (fatty tissue surrounding lobules and ducts).

Breast Cancer originates when these cells of the breast start growing out of control leading to the damage of the structure and complete anatomy of the breast. Mainly cancer develops in the epithelial lining of the breast. The breast cancer can be benign or metastatic. Benign means it doesn't spread to other regions where as metastatic breast cancer can travel to other regions and can spread and kill the patient. [11]

When we compared Figure 3 and Figure 4, it clearly marked the difference between the normal breast and abnormal breast or cancerous breast. It is estimated that the prevalence of breast cancer is as high as the occurrence is estimated to 1 in 8 women worldwide. [13]

CAUSES OF BREAST CANCER

The precise cause factor for breast cancer is still a mystery for the medical science. But among the risk factors associated with breast cancer are Lifestyle of the person, like drinking alcohol and smoking cigarettes. The reason for developing breast cancer is the family history of breast cancer in the immediate family members of the patients. It is estimated that the *BRCA1* and *BRCA2* mutation are among the highest risk factors for developing the disease. Other reasons can be exposure to Sunlight, Hormone replacement therapy and age factor. It is estimated that as the age goes up, it increases the chances of developing the breast cancer. [14]

TYPES OF BREAST CANCER

As more research is going on in the field of breast cancer, many types of breast cancer have been detected. Breast cancer are of types mainly, Ductal carcinoma in situ (DCIS), Invasive ductal carcinoma (IDC), IDC: Tubular carcinoma of breast, IDC: Medullary carcinoma of breast, IDC: Mucinous carcinoma of breast, IDC: Papillary carcinoma of breast, IDC: Cribriform carcinoma of breast, Invasive lobular carcinoma (ILC), Inflammatory breast cancer, Lobular Carcinoma *in-situ* (LCIS), Paget's disease of nipple, Phyllodes tumors of breast, Recurrent and Metastatic Breast cancer & Angiosarcoma of Breast. [15]

CLASSES OF BREAST CANCER DRUGS

Breast Cancer drugs have been classified into, Selective estrogen-receptor modulators (SERM), Aromatase Inhibitors, Biological response modifiers and other Hormonal Therapies. The classification have been described in Table 2. [16]

The Selective estrogen receptor inhibitors are class of drugs that mimic the hormone estrogen. Breast cancer cells depend on estrogen to grow and enlarge. When the receptors of the estrogen in the cells get blocked with the help of SERM's the cancer cell starve to death.

Aromatase Inhibitors work by blocking the production of estrogen in the body, once the estrogen levels are lowered, it will starve the cell to death. Biologic response

Table 2: Classification of Breast Cancer Drugs [16]

Class	Drugs
Selective estrogen receptor modulators	Tamoxifen, Evista (raloxifene), Fareston (Toremifene)
Aromatase Inhibitors	Aromasin (Exemestane), Femara (Letrozole), Arimidex (Anastrozole), Megace (Megestrol)
Biologic response modifiers	Herceptin (Trastuzumab)
Other Hormonal therapies	Zoladex (Goserelin Acetate), Faslodex (Fulvestrant)

Table 3: Phytochemicals Effective Against Breast Cancer [20]

Agents	Active Contents	Effects
Alkaloids	Berberamine	Anti-mammary cancer
	camptothecin	Anti-mammary cancer
	rescinnamine	Anti-mammary cancer
	tomatidine	Anti-mammary cancer
Coumarins	Bergapten	Anti-breast cancer
	Cnidilin	Anti-breast cancer
	Dicoumarol	Anti-breast cancer
	Notoptol	Anti-breast cancer
	Psoralen	Estrogen like activity
	Quercetin	Estrogen like activity
Flavonoids and Polyphenols	Baicalin	Anti-breast cancer
	Scutellarin	Anti-breast cancer
	Resveratrol	Interfering PI3K pathway
	Curcumin	Inhibit transcript of VEGFR and b-FGF
Terpenoids	Parthenolide	Anti-breast, anti-cervical cancer
	Ursolic acid	Anti-breast cancer
Quinone and Other Chemical Classes	Plumbagin	Anti-breast cancer
	Artemisinin	Anti-breast cancer
	Artemisunate	Anti-breast cancer

modifiers work by binding to the protein on breast cancer cells thus leading to their death. Other Hormonal therapies work by same mechanism of blocking the estrogen production leading to restricting the cancer cell growth. [16] Another class of drugs used to treat Breast cancer are the chemotherapeutic agents. The chemotherapeutic agents used to treat Breast cancer are, a) Anthracyclines: They deform DNA structure of Cancer cells, e.g., Adriamycin (Doxorubicin), Ellence (Epirubicin), b) Taxanes: They prevent cancer cells from dividing, e.g., Taxol (Paclitaxel), Taxotere (Docetaxel), c) Alkylating agents: They destruct the DNA of cancer cells, e.g., Cytosan (Cyclophosphamide). [17]

TRADITIONAL MEDICINES TO CURE BREAST CANCER

Traditional medicines dates back to more than 3000 years old and is in existence even before the modern medicines available as treatment options for the mankind.

The plants effective against Breast cancer, or having anti-breast cancer potential are, *Emblica officinalis*, *Aegle marmelos*, *Vernoniaanthelemintica*, *Argemone Mexicana*, [18] Echinacea, Licorice, Garlic (*Allium sativum*), Flaxseed (*Linum usitatissimum*), Turmeric (*Curcuma longa*), Burdock (*Arctium lappa*), Carotenoids, Green tea, Ginseng, Black cohosh (*Cimicifuga racemosa*). [19]

Phyto-chemicals from plants having effective action against breast cancer are described in Table 3.

BREAST CANCER MARKERS

BRCA 1 and *BRCA 2* are the two most used markers for the presence of breast cancer in the human body. In actual

BRCA1 and *BRCA2* are breast region genes which produce a specific kind of proteins which are mainly tumor suppressor proteins. *BRCA 1* and *BRCA 2* are important genes for the proper homeostasis of breast region function. When mutations occur in the genes i.e. specifically *BRCA 1* and *BRCA 2*, it is unable to control the growth and spread of breast cells, thus results into cancer. Therefore the detection of these two genes are accurate markers for the breast cancer. [21]

Another tumor marker are CA 15-3/ CA 27.29. The tissue analyzed for the detection of CA 15-3/ CA 27.29 is blood and helps in the detection of breast cancer. [22]

BREAST CANCER MARKET

According to reports it is estimated that the Global breast cancer market is on the growth path. It is seen to grow from \$ 55.5 million to \$ 7,853.1 million dollar market by 2023 with Compounded annual growth rate of 58.3 % from 2015 to 2023. It is believed that Breast cancer patients would rise from 1.2 million in 2013 to 1.4 million by 2023 in countries mainly US, France, Germany, Italy, Spain, UK, Japan, China and Brazil. The Breast cancer market in these nine countries would rise from \$ 9.8 Billion to \$ 18. 2 Billion From 2013 to 2023. During market research on the revenues generated by the different drugs, it was found that Roche's Herceptin topped the charts followed by Novartis's Afinitor (Everolimus), AstraZeneca's Faslodex (Fulvestrant), Roche's Avastin (Bevacizumab), Novartis's Femara (Letrozole), Roche's Perjeta (Pertuzumab), Cellegene's Abraxane (Nab-paclitaxel), Eisai's Halaven

(Eribulin), GSK's Tyverb/ Tykerb (lapatinib) and Roche's Kadcyla (ado-trastuzumabemtansine).^[23]

NEWER CHEMOTHERAPEUTIC DRUGS

Newer class of drugs have been developed which would target the BRCA mutations, thus the newer class of breast cancer drugs would be targeted therapeutics. The drugs which would target:

1. HER2 receptor include Herceptin (Trastuzumab), Perjeta (Pertuzumab), Kadcyla (Ado-trastuzumabemtansine) and Tykerb (Lapatinib).
2. Anti-angiogenesis drugs: Avastin (Bevacizumab). This drug target angiogenesis in cancer cells, angiogenesis is the nourishment of cancerous cells with the blood vessels. Once these process is blocked it would result in death of cancer cells, thus, are effective therapeutics.
3. Other drugs: Everolimus (Afinitor) is a targeted therapy drug that seems to help hormone therapy drugs work better. It is approved to be given with exemestane (Aromasin) to treat advanced hormone receptor-positive breast cancer in post-menopausal women. It has also been studied with other hormone therapy drugs and for treatment of earlier stage breast cancer. In one study, letrozole plus everolimus worked better than letrozole alone in shrinking breast tumors before surgery. It also seemed to help in treating advanced hormone receptor-positive breast cancer when added to tamoxifen. Everolimus is also being studied in combination with chemotherapy and the targeted drug trastuzumab. Other drugs like everolimus are also being studied.^[24]

CLINICAL TRIALS

Clinical trials are trials which are carried out on humans to search for newer therapies for the particular disease for which the current known therapeutics are not much effective or to search for more effective and advance therapeutics.

Current status of Clinical Trials happening in the field of Breast cancer are:

1. Mint 1 Multi-institutional neo-adjuvant therapy MammaPrint Project 1: The status of clinical trial is Active. It is in Phase Four of its study and involves participants of age 18 and above.
2. Safety and efficacy study of the Xofigo, Xofigo IORT system: The trial is in Phase IV and is Active. It involves participants of Age 40 and above. The basic aim of this study is to find treatment modalities for breast cancer. IORT stands for Intra-operative radiation therapy.
3. MM-302 Plus Trastuzumab vs. Chemotherapy of Physicians choice plus trastuzumab in HER2-Positive locally advanced / Metastatic Breast cancer patients: Trial status is Active. It is Phase II/Phase III stage. It involves participants of age 18 and above. The study is open label trial, randomized study of MM-302 plus trastuzumab.
4. A study to compare the safety and efficacy of an Aromatase inhibitor in combination with Lapatinib, Trastuzumab or both for the treatment of Hormone

receptor Positive, HER 2 + Metastatic Breast Cancer: The trial status is Active. It involves participants who are post-menopausal and have stage IV metastatic breast cancer.

5. Tamoxifen citrate, Letrozole, Anastrozole, or Exemestane with or without Chemotherapy in treating patients with invasive RxPONDER Breast Cancer: The current trials status is active. It is in phase III of Clinical Trial and involves participants of age 18 and above. At present more than 350 clinical trials in active state are being carried out on Breast cancer.^[25]

CONCLUSION

Breast cancer is one of the leading cause of morbidity and mortality for the women across the globe. With an estimate of 1 out of every 8 women to be likely detected with breast cancer, the menace of Breast cancer is increasing at an alarming rate. It is though a not so good news if the public health is concerned, on the other hand it's one of the niche areas of growth and development for the pharmaceutical and drug industry. The earlier the detection of the breast cancer, the better are the chances of 5 year survival rate after the chemotherapy or any therapy. Thus more and more agents shall be searched in to restrict the growth of cancer at it early stage. Only then the overall research in the same field will be beneficial for the mankind.

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