

NOVEL APPROACHES IN BREAST MALIGNANCY TREATMENT

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Abstract: Breast cancer is second leading cancer in women and approximately one in eight women being affected by breast cancer in India. The finest breast cancer therapies are targeting oestrogen receptor, HER2 receptors, surgical management and chemoprevention strategies. But all breast tumors do not respond to the above mentioned therapies so now targeted therapeutic approaches are used such as evading apoptosis, molecule targeting therapy, tissue invasion and metastasis.

Keywords: Breast cancer, Lymphocytes, Lymphatic tubes, Molecular targeting therapy, Oestrogen receptor, Sternum

INTRODUCTION

The Breast consists of connective tissue, fat, and glandular tissue (contain milk gland). Breast milk is produced in lobes or milk gland, which is connected to the nipple by network of milk ducts. Size of breast become smaller and feel softer as the women gets old [1].

Lymphatic tubes (ducts) are connected to lymph nodes by a network, which is present beside the breastbone and behind the collarbones. Lymph fluid flows from lymphatic system and contains cells called lymphocytes (body's natural defense), which fight against infections and diseases^[1].

Human breast tissue begins to develop in the sixth week of foetal life and breast duct begin to grow after one to two years of menstruation begins. Breast tissue extends from the edge of the sternum to the midaxillary line. Internal mammary artery, which runs underneath the main breast tissue, is responsible for blood supply in breast. Lymphatic vessels flow blood in opposite direction in breast. At the birth, the breasts of both male and female are not well developed. Areola becomes a prominent bud and breast begins to fill out in case of early puberty. In late puberty areola becomes flat and fat increases in breast. Female breast contains similar structures of male breast except glandular tissues, acini, ducts, cooper's ligaments and Montgomery's glands^[2]

External anatomy of breast consists of nipple, areola, Montgomery's glands, morgagni's tubercles, skin, axillary's tail, inframammary fold and the margin of the pectoralis major muscle.

Internal anatomy of breast consists of fascial layers, fibrous tissue, glandular tissues, retro mammary

*Corresponding Author: Dr. Radha Goel, Assistant Professor, I.T.S Paramedical College, Delhi-Merrut Road, Ghaziabad, Uttar Pradesh-201206. India. space, adipose tissue, cooper's ligament, pectoral muscle, circulatory system and lymphatic channels³. (Figure – 1A)

Breast Cancer is found in both male and female but predominantly affects females. Cancer is disease of overgrowth of cells. In case of breast cancer, there is formation of lumps or tumour in breast due to overgrowth of the cells lining the breast ducts^[1].

Receptors Responsible For Breast Cancer:

There are particular receptors on cancer cells which examine the tissue which is removed during surgery. Two types of receptors are responsible for the breast cancer.

 Hormonal receptor: Oestrogen and progesterone hormone receptors are present in cancer cells. Presence of significant number of receptors is known as oestrogen receptor positive breast cancer. If not, it is known as oestrogen receptor negative^[3, 4]. (Figure – 2A)

Figure – 1A: Anatomy of breast



2) Protein Receptors: Protein human epidermal



growth factor 2 (HER2) is present on breast cancer cell and if it is present in high amount then it is known as HER2 positive breast cancer [5,6]. (Figure: 2B)

Figure: 2A: ER Positive



Figure:2B: HER2 Positive



Types of Breast cancer: It is generally of two types **1) Noninvasive (in situ) breast cancer:**

- Ductal non-invasive: Cancer cells have not spread to breast tissue around the duct or lobules.
- b) **Lobular non-invasive:** Abnormal cells in the milk-producing glands of the breasts are present and rarely spread outside of the lobules to other parts of the breast.

2) Invasive breast cancer:

- a) Ductal invasive carcinoma: It begins in milk duct but spreads to normal or healthy tissue inside the breast.
- **b)** Lobular invasive carcinoma: It begins inside the lobules but spreads to normal tissue inside the breast^[6].

Signs and symptoms of breast cancer

- 1) Breast pain and heaviness
- 2) Swelling, thickening, redness in the breast skin
- 3) Bloody discharge from nipple^[7] (Figure-3A)

Pathogenesis:

There are following risk factor for cancer:

1) Age: Risk of developing breast cancer increases with age. About 1 out of 8 offensive breast cancers

are found in women younger than 45, while about 2 of 3 offensive breast cancers are found in women age 55 or older.

- 2)Hormonal factor: Using combined hormone therapy (oestrogen and progesterone) after menopause increases the risk of getting breast cancer.
- 3)**Genetic factor**: Inherited mutations also increase the risk for developing breast cancer. BRCA:1 (Breast cancer:1) and BRCA:2 (Breast cancer:2) genes are responsible for hereditary breast cancer.
- 4)**Alcohol:** Excessive alcohol consumption enhances the risk of developing breast cancer.
- 5)**Obese**: After menopause most of oestrogen comes from fat tissue. Having more fat tissue raises oestrogen levels and augments the chances of getting breast cancer.
- 6)Not having children or not having breastfed: Risk of breast cancer slightly increases in women who have no children or who had their first child after age 30.
- 7)**Antiperspirant:** Chemicals which used as antiperspirants are absorbed through the skin and interfere with lymph circulation, which causes toxins and eventually lead to breast cancer.
- 8)Environmental factors: Compound which present in environment such as some plastics, certain cosmetics, personal care products, pesticides, and PCBs (polychlorinated biphenyls) influence on breast cancer risk^[8,9].



Figure.3A: Symptoms of breast cancer

Stages of Breast Cancer: There are totally four stages of breast cancer^[10] as shown in Table.1.

Table.1:	Stages	of	breast	cancer
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1)	Stage o	Carcinoma in situ (survival rate = 93%)
2) 3)	Stage 1 Stage 2 a	Tumour = 2cm (survival rate = 88%) Tumour = 2 – 5 cm, spread to auxiliary nodes (survival rate = 81%)
4)	Stage 2 b	Tumour is greater than 5 cm. (survival rate = 74%)
5)	Stage 3 a	Lumps under 5 cm and spreaded in lymph node (survival rate = 67%)
6)	Stage 3 b	Spread to tissue near to breast surrounding skin and muscle (Survival rate = 41%)
7)	Stage 3 c	Affected lymph nodes under collarbone, under arm and tissue near breast (Survival rate = 49%)
8)	Stage 3 d	Divided into operable and inoperable stage.
9)	Stage 4	Affected other parts of body mostly lungs, liver, and brain (survival rate = 15%)^{[10]}

Screening Of Breast Cancer:

Early detection of breast cancer depends upon age of women. Several methods are used for screening such as mammography, magnetic resonance imaging, fine needle aspiration, biopsy, wire localization, blood test, clinical breast examination, computer aided detection.

1) **Mammography:** In this case early detection is possible with the help of low dose of X - rays, and visualization of internal structure of breast is possible. Not possible to detect all types of breast cancer with the help of mammography^[11].

2) **Magnetic Resonance Imaging (MRI):** In this method gadolinium DTPA (Diethylenetriamine Pentaacetic Acid) is injected into the small vein in the arm before examination and magnetic field is used in the place of X-rays. It is very expensive than mammography and this is only disadvantage of MRI^[12].

3) **Fine Needle Aspiration (FNA):** In this technique fine needle is used to withdraw some cells from lumps and it is a painful process. These cells are sent to the laboratory for examination ^[13].

4) **Biopsy:** There are different types of biopsy:

Needle biopsy: Small piece of tissue is taken from the lump with the help of needle and then it is examined under a microscope.

Excision biopsy: In this method size of lump is determined with the help of mammogram^[14].

Vacuum assisted biopsy: This method is little similar to needle biopsy technique. In this method vacuum is used to pull tissue from lump with the help of high speed rotating knives. Radiopaque is used as marker at the site^[15].

5) **Wire Localization:** Very small wire is used at the time of X: ray or ultrasound for marking the exact area. After

X-ray it is removed and the cut is covered with the small dressings^[16].

6) **Blood Tests:** Sample from the blood is withdrawn and number of cells and tumour markers are counted but this method is not commonly used^[17].

7) **Clinical Breast Examination (CBE):** The annual CBE is important for women above the age of 40 years. The pads of fingers above undressed breasts are kept and feel the shape, texture, location and position of lumps. Also examine the area of both underarms and notice dimpling and redness on breast^[17].

8) **Computer Aided Detection and Diagnosis (CAD):** The image of lumps is converted into signal and then analyzed by computer^[18].

9) **Nipple discharge exam** – The discharge from nipples is collected and examined under microscope for cancerous cell. Mostly nipple discharge is not cancer [18].

TREATMENT

A) Foods:

1) **Flaxseeds:** The omega:3s, linens, and fibre forms a protective layer against cancer cells and these three things are present in flax. It can get in the form of whole seed or flaxseed oil.

2) **Brazil Nuts:** It contains selenium, fibre, and photochemical which helps to fight against inflammation, tumour growth and improves the immune system and can also be taken with asparagus, which contain anti – cancer agents.

3) **Pomegranates:** It contains polyphone and anti: oxidants. It is highly recommended in breast cancer as it prevents the growth of cancer cells.

4) **Dark: Green Leafy Vegetables** – Dark green leafy vegetables contain fibre, vitamin B, photochemical, chlorophyll which are responsible to off cancerous cells, so it is good to add some vegetables in daily diet.

5) **Garlic:** It is a best source of cancer fighting compound and also known to retard the tumour growth ^[19].

B) Surgery: Surgery is used to remove cancer from breast (lumpectomy) or too remove whole breast (mastectomy) from body. But after lumpectomy it is required to take radiation therapy for some time because there are possibilities of reoccurrence of cancer in breast. And in case of mastectomy whole breast is removed with lymph nodes under the arm but there are options of breast reconstruction. For reconstruction soft plastic (silicon) or tissues from other parts of body is used. Possible side effects of surgery are temporary swelling, tenderness, forms hard scar tissue in the surgical site. Bleeding and infection at the surgery site are also possible^[20].

C) Radiation Therapy: Radiation therapy is important part of breast cancer treatment; it's used after surgery for destroying residual breast cancer or for shrinking the tumour before surgery. It mainly damages the double standard DNA of tumour cells by IR radiation^[21].

Two types of radiation therapy:

a) **External beam radiation:** This method depends on size and extent of cancer and in this the beams are focused from machine onto the affected area. Time period of this therapy is 5:6 weeks. Swelling and heaviness in breast are main short term side effects of external beam radiation therapy^[22].

b) **Internal radiation therapy (Brachytherapy):** In this therapy radioactive substance, sealed into needle or catherates are placed into the cancerous area. There are two types of brachytherapy Interstitial brachytherapy and Intracavitary brachytherapy^[22].

D) Chemotherapy: This involves treatment with cancer killing drugs which are generally given by IV or oral route^[23]. In this category drug combinations are given to avoid possible side effects. Chemotherapy based upon size of tumour, lymph nodes, and presence of ER receptor and HER2 receptor. It may be used before surgery for shrinking the tumour or after surgery for reducing the chance of cancer coming back.

Common side effects of chemotherapy include tiredness, feeling weak, a sore mouth, hair loss, loss of appetite and feeling of malaise^[24, 25, 26].

Drug combinations in chemotherapy are:

CMF: Cyclophosphamide, Methotrexate, and 5-fluorouracil (fluorouracil, 5-FU)

CAF (or FAC): Cyclophosphamide, Doxorubicin (Adriamycin), and 5-fluorouracil

AC: Adriamycin (Doxorubicin) and Cyclophosphamide

EC: Epirubicin and Cyclophosphamide

TAC: Docetaxel, Adriamycin, and Cyclophosphamide

 $AC \rightarrow$ Adriamycin and Cyclophosphamide followed by Paclitaxel or Docetaxel (Taxotere). Trastuzumab (Herceptin) may be given with the Paclitaxel or Docetaxel for HER2/neu positive tumours.

 $A \rightarrow CMF$: Doxorubicin (Adriamycin), followed by CMF

CEF (FEC): Cyclophosphamide, Epirubicin, and 5-fluorouracil (this may be followed by Docetaxel)

TC: Taxotere (docetaxel) and cyclophosphamide

TCH: Docetaxel, Carboplatin, and Trastuzumab (Herceptin) for HER2/neu positive tumours $^{\left[^{23}\right] }.$

E) Hormonal Therapy

a) If ER receptor positive:

1) Tamoxifen and Toremifene: Tamoxifen and Toremifene are anti-oestrogen drugs. These drugs are preventing the binding of oestrogen by blocking oestrogen receptor on breast cancer cells. The most common side effects of these drugs are fatigue, hot flashes, vaginal dryness, mood swings and also increase the risk of heart attack in women $[^{27,28}]$.

2) Aromatase inhibitors (Als): Three drugs letrozole, anastrozole, and exemestane inhibited the production of oestrogen by blocking the aromatase enzyme in fat tissue which is responsible for oestrogen secretion in post: menopausal women. Als are only effective in post: menopausal women.

In case of premenopausal women goserelin acetate is generally preferred. It lowers the level of oestrogen and stops menstruation, given once in a month. Feeling sick, joint pain, weight gain, and vaginal discharge are common side effects of drugs which are used in hormonal therapy^[29].

b) If HER2 receptor positive:

1) Trastuzumab (herceptin) knows as monoclonal antibody, it binds on HER2 receptor present on breast cells and inhibits the growth of cancer cells and stimulates immune system. Common side effects of herceptin are: heart problems, rashes, itching, headache, feeling sick^[30].

2) Pertuzumab: Pertuzumab is also a monoclonal antibody that attaches to the HER2 protein. Hair loss, nausea and fatigue are common side effects of pertuzumab^[31].

F) Ovarian ablation: Ovaries are removed by surgery if the level of the oestrogen is high (Oophorectomy). Luteinizing hormone-releasing hormone (LHRH) analogues, such as goserelin or leuprolide are used in ovarian ablation. Dry skin, depression, and emotional changes are common side effects of this treatment^{3[32]}.

G) NSAID'S: Aspirin, Ibuprofen, Sulindac, and Celecoxibe are used as chemo preventive drug. NSAID'S inhibit the growth of cancer cell by inhibiting COX:1 and COX:2 enzyme^[33, 34]

H) Telomerase and Telomerase inhibitors: Telomerase is a reverse transcriptase complex required for cell division and growth. Anti: telomerase are more effective and less toxic than other chemotherapy. Telomerase inhibitors reduce the activity of telomerase and inhibit the proliferation of cancer cell. Duration of this therapy is one month to few ^[35, 36].

I) Epidermal growth factor: Anti: ErbB: 2 monoclonal antibody or ErbB: 2 tyrokinase inhibitor (Trastuzumab) inhibits the cell proliferation by inhibiting the action of epidermal growth factor. It is not used alone, causes

resistant in ER receptor therapy^[37]. Mostly it is used in combination with taxanes.

J) Ayurvedic cow urine therapy: Cow urine is used in the treatment of cancer because it has ability to improve efficacy and absorption of anti – cancer drugs. Cow urine enhances the anti – microbial effects of antibiotic and anti-fungal agents so it reduces the side effects of antibiotics. Component of cow urine (benzoic acid, hexanoic acid, ammonia, anti: oxidants) used for protecting DNA from oxidative damage. Cow urine also possesses anti-tumour quality, anti-oxidants and antibacterial quality^[19].

Treatment of breast cancer in pregnancy: Radiation therapy is not used because it increases the birth defects. Mainly breast conserving surgery is referred^[19].

CONCLUSIONS

There are multiple causes of breast cancer such as age, family history, late menopause, under wire bras, and antiperspirants. Abortion is also a major cause of developing cancer. At present there is no permanent treatment of breast cancer, it depends upon early detection of cancer. But day by day researchers have found newer treatments and strategies for combating breast cancer. Breast cancer is a complex disease and different molecular target therapy is involved in the treatment. The success of current strategies encouraged the use of newer approaches. Novel strategies contain telomerase inhibitor, chemoprevention, molecular targeting, radiation therapy, and EGFR tyrosine kinase inhibitors. Education about breast cancer, care, hope inspiration and mental support is indispensable for a cancer patient.

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