International Journal of Science and Research Archive

eISSN: 2582-8185

Cross Ref DOI: 10.30574/ijsra

Journal homepage: https://ijsra.net/

(REVIEW ARTICLE)

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A concise review on breast cancer in pregnancy

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International Journal of Science and Research Archive, 2023, 08(02), 475–491

Publication history: Received on 23 February 2023; revised on 01 April 2023; accepted on 04 April 2023

Article DOI: https://doi.org/10.30574/ijsra.2023.8.2.0272

Abstract

Breast cancer is major serious cancer in the women, it can be easily treated with chemotherapy drugs or by breast conservation surgery if it is diagnosed earlier. However the condition become even worse in those pregnant women, because chemotherapy is the most common first line prophylaxis treatment for breast cancer. In pregnancy diagnosed with breast cancer reveals a complicated chemotherapy because it affect the fetus and eventually produce fetal abnormalities and decreases the survival chances of fetus. The 50% survival chances of breast cancer patient is increased with the early diagnosis. Hormonal factors like estrogen, inheritance of BRCA1 and BRCA2 are the foremost responsible for breast cancer, it can get even worsen due to life style adaptations. Multi-drug resistance is eventually happen due to prolonged chemotherapy.

Keywords: Breast cancer; BRCA1 and BRCA2; Estrogen; Chemotherapy

1 Introduction

Breast cancer in pregnancy is a very rare condition, occurring in only about 1 out of every 10,000 pregnancies [1]. However, it is important to be aware of the symptoms and risk factors for this condition, as it can be life-threatening if not detected early. The most common symptoms of breast cancer in pregnancy is a lump or mass in the breast tissue. Other possible symptoms include nipple discharge, changes in the appearance of the nipple or breast skin, and pain in the breast. There are several risk factors for developing breast cancer during pregnancy [2]. These include a family history of the disease, previous history of breast cancer or other cancers, exposure to radiation, and certain genetic mutations. Having one or more of these risk factors does not mean that you will definitely develop breast cancer, but it does increase your chances [3]. If you are diagnosed with breast cancer during pregnancy, there are treatment options available that can help you and your infant. Surgery is often recommended as the first step in treatment, followed by chemotherapy and/or radiation therapy [4,5]. You will also likely be monitored closely during your pregnancy to ensure that the cancer does not spread. With proper treatment, many women with this condition go on to have healthy pregnancies and deliver healthy babies [6].

2 TNM classification

This method is common for all types of cancer. The cancer cells are classified according to the tumour size and its nature about how it is transferred to other organ tissue (metastatis).

- T – denotes the tumour where it is originated (or) evolved – it is called as primary tumour)
- N- denotes whether the cancer spread or occupied near by lymph node or not.

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- M – It shows the cancer is metastatized -it defined as the cancer cell move from one place (primary origin) to another place and proliferation takes place to create secondary cancer [7].

2.1 The primary tumor (T category) [8]

It shows where the primary tumor start in which organ, size and location.The **T category** can be assigned a letter or a number:

TX denotes the absence of data or measurement for the main tumour**.**

T0 indicates that there is no sign of a primary tumour (it cannot be found).

This indicates that the cancer cells are not spreading into deeper cell layers, but are instead solely growing in the layer of cells where they initially appeared.

The size of the tumour and/or the extent of its dissemination into neighbouring structures may be indicated by a number (such as T1, T2, T3, or T4) following the letter T.

The tumor's size or the extent to which it has encroached on neighbouring tissues is correlated with the tumor's T number.

2.2 The lymph nodes (N category) [9]

NX denotes the inability to assess the adjacent lymph nodes.

N0 denotes the absence of malignancy in any adjacent lymph nodes.

The size, position, and/or quantity of neighbouring lymph nodes impacted by cancer may be indicated by the numbers after the letter N (for example, N1, N2, and N3).

The extent of cancer spread to neighbouring lymph nodes increases with increasing N numbers.

2.3 Metastasis (M category)[10]

Metastatis is defined as the cancer cell detach from the primary tumor enter into blood and lymphatic system travels and produce a malignant secondary cancer on different organ or tissue.

The M category is assigned a number:

- M0 means that no distant cancer spread has been found.
- M1 means that the cancer has been found to have spread to distant organs or tissues.

2.4 Stages of breast cancer

There are four stages of breast cancer depending on the size of the tumor, intensity of penetration, invasive or non – invasive and metastatic nature of an cancer cell.

2.4.1 Stage 0 [11]

This is the starting stage of a breast cancer. The cancer cell begins to grow within the territory region does not get involved or penetrated into near by adjacent cell. For example, DCIS (Ductal Carcinoma In Situ- the cancer cell start to grow inside the milk duct doesn't emerge out. It is an very first early stages of cancer where the cancer can be treated effectively by chemotherapy.

2.4.2 Stage 1

In this stage , breast cancer is microscopic invasive around tissue .It has two categories 1A and 1B[12].

- Stage 1A – emergence of cancer cell is breast and does not penetrate in adjacent lymph node, size measure upto 2 cm .
- Stage 2B - cancer cell found in the lymph node and its size larger than 0.2mm [13].

2.4.3 Stage 2

There are also two categories in Stage 2: 2A and 2B. Stage 2A depicts a tumour that is identified in the sentinel or axillary lymph nodes but not in the breast. The tumour can range in size from less than 2 cm to more than 5 cm. Stage 2B, however, states that the tumour may exceed 5 cm in size but cannot reach the axillary lymph nodes [14].

2.4.4 Stage 3

Three subcategories—3A, 3B, and 3C—have been established within it. There are two stages of breast cancer: stage 3A and stage 3B[15]. Stage 3A describes that no tumour is found in the breast, but it may be found in 4–9 axillary lymph nodes or in sentinel lymph nodes. Stage 3B describes that the tumour may be of any size, but it may have caused swelling or an ulcer on the breast skin, and it may have spread to up to 9 axillary lymph nodes or to sentinel lymph nodes [16]. Having red, heated, and swollen breast skin is indicative of stage 3B, which is an inflammatory form of breast cancer. Stage 3C, however, represents a tumour that has progressed to at least 10 axillary lymph nodes and possibly more [17].

2.4.5 Stage 4

In this stage the cancer is metastasized and spread into several other organs like liver, lung, pancreas etc., The mutated cancer cell proliferate uncontrollably their tumour size increasing after the stage-1 the blood cell forms around the tumour cell (Angiogenesis) feeding the nutrition nourishes tumour growth and the metastatic cancer cell hide themselves from the immune system i.e the cancer cell release an specific type of proteins that prevent them from immune attack [18,19].

3 Types of breast cancer

Breast cancer types can be determined by determining whether specific cells, such as breast ductal tissue or epithelial cells, become malignant in the breast region.

3.1 Ductal or lobular carcinoma

The majority of breast cancers are carcinomas, which are tumours that develop from the epithelial cells that line the body's organs and tissues. Adenocarcinoma, a more specific type of carcinoma that begins in cells in the ducts (the milk ducts) or the lobules, is typically the type of carcinoma that develops in the breast [20].

3.2 Invasive ductal carcinoma (IDC)

In this type the cancer cell spread in to the ductal region where the milk pass from the lactocytes into alveoli lumen then into the nipple. This type is termed as Invasive ductal carcinoma [21].

3.3 Lobular carcinoma in situ (LCIS)

A condition known as lobular carcinoma in situ (LCIS) occurs when abnormal cells are discovered in the breast's lobules [22]. The surrounding breast tissue has not been invaded by the abnormal cells outside of the lobules. LCIS rarely develops into invasive carcinoma and is very curable [23].

3.4 Invasive Lobular Cancer (ILC)

Invasive breast cancer that spreads to neighbouring healthy tissue after beginning in the lobules (milk glands) of the breast [24]. The lymphatic and blood systems are other routes by which it might spread to other body parts[25].

3.5 Triple Negative Breast Cancer

Triple-negative breast cancer is characterised by the absence of the HER-2/neu gene, progesterone, and oestrogen, the three most prevalent types of receptors known to promote the formation of most breast cancers [26]. This indicates that tests for the hormone receptors HER-2, ER, and progesterone receptors on breast cancer cells have come back negative (PR) [27].

3.6 Inflammatory Breast Cancer (IBC)

Breast cancer that has invaded the epidermis and lymphatic vessels of the breast is referred to as inflammatory breast cancer [28]. It frequently results in no clear tumour or lump that is localised in the breast and can be felt. However, symptoms start to show up when the breast cancer cells obstruct the lymph veins [29].

3.7 Metastatic Breast Cancer [30]

The term "metastasis" is often used to describe the spread of a malignant tumour from its initial or main site to another, secondary site inside the host's body.

4 Factors involved in breast cancer

4.1 Hormonal factors responsible for breast cancer

Estrogen is very much important in the development of secondary sexual characters like enlargement of the breast by accumulation of fat beneath the breast skin, elongation of the cervical bone which changes in overall body characters [30]. Estrogen is an natural female hormone produced by the ovaries under the influence of FSH and LH (the hypothalamus secrete an gonadotrophin-releasing hormone passed through the hypothalamus hypohyseal pathway stimulates basophils cells gonadotrophs in the anterior pituitary and is inhibited by negative feedback mechanism on their target gland) [32,33]. After childbirth the estrogen are high in the new born child and it decreases as the ageing, the amount of FSH and LH are produce negative feedback mechanism at low concentration, after menarche (the very first menstural phase goes through the women) [34] ,it usually occurs after the age 12 the estrogen and progesterone level are high[35]. In menstural cycle there are two phase proliferative phase and secreatory phase, day 1-6 bleeding phase after the that FSH nourhies the ovaries to produce egg, it has millions of egg of that healthy fully matured egg is release by the graffian follicle [36]. The LH is more important in the rupture of graffian follicle to release the mature egg into the fallopian tubes at the day 14 [37]. The graffian follicle has progesterone producing hormone which releases the progesterone which makes the endometrium (the tremendous supply of blood along the side of endometrium to implant the fertilized egg) if the egg gets fertilized it will get implanted into the endometrium and the corpus luteum continues to secrete progesterone until the labour [38]. If the egg is not fertilized the copus luteum into corpus albicans which lacks in producing the progesterone the endometrium in the uterus will shed the blood at 22- 28 days and the next cycle begin [39]. After menopause (declines of the menstural cycle) propably occurs at the age between 45-50 the reduces in the production of oestrogen and progesterone[40], which leads to cause and postmenopausal symptoms like Irregular periods, Vaginal dryness, Hot flashes, Chills., Night sweats, Sleep problems, Mood changes, Weight gain and slowed metabolism [41]. In order to reduce symptoms the person has to take synthetic estrogen (synthetic estrogen steroids like ethinylestradiol, mestranol, Tibolone and non-steroidal synthetic estrogen like Diethylstilbestrol, hexestrol, dienestrol etc.,). Estrogen alone has increase the incidence risk of the breast cancer and combination like estrogen plus progesterone has low risk of occurrence of the breast cancer[42]. The occurrence of the breast cancer in hormonal or estrogen replacement therapy most likely depend on the duration of the HRT (hormonal replacement therapy). Combined HRT id like estrogen plus progestin need to lower the post-menopausal syndrome but its more likely to be incidence the risk of breast cancer[43].

Table 1 Daily secretion of FSH in men [44]

	Before Puberty	**During Puberty**	**Adult**
Male	0 to 5.0 mlU/mL	0.3 to 10.0 mlU/mL	1.5 to 12.4 mlU/mL

Table 2 Daily secretion of FSH in women [45]

	Before Puberty	**During Puberty**	**After Menopause**
Female	0 to 4.0 mlU/mL	0.3 to 10.0 mlU/mL	25.8 to 134.8 mlU/mL

5 Irradiation of the breast region: [46, 47, 48]

During diagnosis for normal health checkup like chest X-ray, and its radiation absorbed by the irradiated tissue may increase the incidence of genetic alterations like DNA mutation, nucleotide delusion, DNA inversion, and translocation. The increase in the incidence of breast cancer occur in women who has exposed to X-ray for diagnosis before the age 15. It may alter the mutations in $BRCA_1$ and $BRCA_2$ gene which may provoke its altered nature after 30-40 years depends upon the life style and personal family history.

5.1 Life style factors: [49, 50, 51]

Diet and nutrition are controversial factors. Dietary fat has received a great deal of attention as a possible risk factor for breast cancer because of the high correlation between national per capita fat consumption and the incidence of the disease. In addition, a number of experiments in laboratory animals have suggested a link between the amount and type of dietary lipids and the growth of mammary tumors..

6 Family history of breast cancer

Breast cancer is one of the most common and deadly forms of cancer, affecting millions around the world. Mutations in the genes BRCA1 and BRCA2 play a role in breast cancer development [52]. BRCA1 and BRCA2 are the genes they are located on the chromosome 17 mainly present in the breast, uterus, ovaries, pancreas in female and prostate in male. Most normal function of the gene is tumour suppression, they get actively involved in the DNA repair [53]. BRCA1 and BRCA2 are two human genes that produce proteins that help repair damaged DNA. These genes are important for the stability of our cells and the prevention of cancer. However, when either of these genes is mutated, it can no longer perform its function properly. This can lead to an increased risk of breast cancer [54].

There are several different types of genetic mutations that can occur in the BRCA1 and BRCA2 genes. Some of these mutations are more common than others [55]. For example, the most common mutation in the BRCA1 gene is called the 185delAG mutation. This particular mutation is found in about 1 in 500 people of Ashkenazi Jewish descent . Other mutations in these genes are much rarer. For example, there is a mutation in the BRCA2 gene called 6174delT which is found in only 1 in 1,00,000 people. There are also many other rare mutations in these genes that have been identified [56].

The vast majority of people who carry a mutation in either the BRCA1 or BRCA2 gene will never develop breast cancer[57]. However, carrying a mutation does increase a person's risk for developing this disease [58]. The risk is higher for women who have a mutation in the BRCA1 gene than it is for women who have a mutation in the BRCA2 gene[59]. BRCA1 and BRCA2 are two of the most well-known genes associated with breast cancer. Mutations in these genes have been linked to an increased risk of developing breast cancer [60] .

6.1 Mutations in brca1 and brca2 gene [62,63]

BRCA1 and BRCA2 are the two most common types of inherited breast cancer. They are responsible for about 20-25% of all hereditary breast cancers and 5-10% of all breast cancers. Women with a BRCA1 or BRCA2 mutation have a 45-85% chance of developing breast cancer during their lifetime, compared to 12% in the general population. BRCA1 and BRCA2 mutations can be passed down from either parent. In most cases, only one parent need to have the mutation for their child to inherit it. If a woman has a BRCA1 or BRCA2 mutation, her daughter has a 50% chance of inheriting it. Sons can also inherit the mutation, but they are less likely to develop breast cancer than daughters.

7 Diagnosis of breast cancer

Various types of instruments are available for the diagnosis of breast cancer

7.1 Mammography

A mammogram is an X-ray examination of the breast. It is used to detect and diagnose breast disease in women who either have breast problems, such as a lump, pain, or nipple discharge, as well as for women who have no breast complaints. The procedure allows detection of breast cancer, benign tumors, and cysts before they can be detected by palpation (touch)[64]. Mammography has been used for about 30 years, and in the past 15 years technical advancements have greatly improved both the technique and results. Today, dedicated equipment, used only for breast X-rays, produces studies that are high in quality, but low in radiation dose. Radiation risks are considered to be negligible[65].

In mammography , the two sides of the breast are held in an instruments where the parallel plates are compresses the breast to reduce reducing the thickness of the breast eventually minimizes the scattering of the low doses of x-rays which produce better quality of the breast imaging[66]. The breast is photographed from both, a head-to-foot (craniocaudal, CC) and an angled side-view (mediolateral oblique, MLO) angle. The two different sorts of mammography investigations are screening mammograms and diagnostic mammograms [67,68]

7.2 Ultrasound breast imaging

It is a noninvasive medical procedure, painless and safe. Sound waves are used to create images of the inside of the body. Sonography is another name for ultrasound imaging. It makes use of skin-contact gel and a tiny probe known as a transducer. The probe emits high-frequency sound waves that pass through the gel and into the body. The probe gathers the sounds that are reflected back[69]. To produce an image, a computer uses those sound waves. Radiation-free ultrasound exams are available (x-rays). Because ultrasound records images in real-time, it may display the inside organs' shape and motion. Additionally, blood may be seen moving via blood arteries in the photos[70].

7.3 Magnetic resonance imaging (MRI)

A thorough, cross-sectional image of interior organs and structures can be produced by an MRI scan using a powerful magnet, radio waves, and a computer. It uses electromagnetic radiation to visualize the interactions between organs or to capture the characteristics of a tissue that contrast with the pre-installed characteristics of the human body, such as cells, tissues, etc[71]. Because MRI does not use ionising radiation, which is hazardous to the human body and can damage DNA or inactivate tumour suppressing agent, making it more effective than mammograms and X-rays[72].

The patient should be administered IV drip of gadalonium constrast media- it is a chemical substance utilised in magnetic resonance imaging (MRI) scans. Gadolinium contrast medium, when administered intravenously, increases and improves the quality of the MRI images (or pictures)[73-75]

7.4 Biopsy

To make sure the accurate diagnostic result to avoid the false negative report biopsy is untaken by the physician. Biopsy is an procedure to remove the cancer or abnormal cell from the body assisted by using an MRI, ultrasound imaging and mammograms.it has several types fine needle biopsy, core biopsy, surgical biopsy [76].

7.4.1 Fine needle biopsy

It is done by fine needle to prickle a lump or abnormalities in the lymph node. Ultrasound is used to guide the prickle during biopsy [77].

7.4.2 Core biopsy

In this biopsy, a wide needle is used to prickle the breast lumb or abnormalities. It is actually done to obtain some mass of tissue from the region of abnormal or cancer cell. This is done under the proper anaesthetic agent provided to the patient [77] .

7.4.3 Surgical biopsy [79]

In this procedure the physician made an incision to affect area and remove an mass of tissue or breast lump for possible breast cancer diagnosis. Prior to biopsy general anesthetic are given according to patient condition guided by ultrasound image scanning, MRI or mammograms.

7.5 Computed tomography

The noninvasive medical treatment known as computed tomography (CT), sometimes known as "computerised tomography" or "computed axial tomography" (CAT), creates cross-sectional images of the body using specialised X-ray equipment [80]. There are numerous diagnostic and therapeutic uses for these cross-sectional pictures. Every part of the body can get a CT scan for a variety of purposes (e.g., diagnostic, treatment planning, interventional, or screening). The majority of CT scans are done as outpatient surgeries[81].

8 Prophylaxis involved in breast cancer

8.1 Surgery for breast cancer

8.1.1 Breast conserving surgery

In this type the cancer affected area alone is surgically removed by using appropriate general anaesthetics. This is done by well performing physician (surgeon). The segment of the dissection region is depend upon the size and how far the cancer spreads.it is also known as lumpectomy[82,83].

8.1.2 Sentinel lymph node biopsy (SLNB) [84, 85]

In this procedure firstly the patient is anaesthetized and isophane blue (In selective sentinel lymph node biopsy, the dye isosulfan blue is commonly implemented. It possesses two sulfonic groups in its chemical composition since it is a patent blue isomer, and this allows for some protein binding in lymph and plasma) is injected around the areola (a dark circle around the nipple) followed by massaging of the breast [85]

8.1.3 Axillary lymph node dissection (ALND)

The lymph nodes in the armpit are removed during a cancer therapy and this procedure known as an axillary lymph node dissection, also known as an axillary node dissection or an axillary lymphadenectomy[86,87].

8.2 Radiation for breast cancer [88,89]

Radiation therapy is an treatment by using an high intensity x-rays to destroys an cancerous pathetic cell but the most disadvantage is normal cell or its genetic material gets altered like deletion, insertion, translocation and provoked into an new cancerous environment.

After mastectomy (or) breast conserving surgery there is an chances of leftovers cancerous cell behind the lymph nodes, in that situation radiation therapy is used to destroy the oncogenic cell[90,91].

8.3 Chemotherapy for breast cancer:

Generally, chemotherapy are a drug used for the treatment of all type of cancer. Anti-cancer drugs which are administered intravenously to pass through the blood stream and reach the tumor cells and destroy it[92,93]. Sometimes cancer may spread into the other part of the body like spinal cord, brain tissue in that case the drug is administered through intrathecal route. Intrathecal is a spinal cord where the cerebrospinal fluid is present. It can travel through spinal cord and brain. Mostly chemotherapy drug for cancer treatment are combination of 2 or 3 to give effective treatment[94,95].

8.4 Chemotherapy drugs used for breast cancer

8.4.1 Cyclophosphamide [96]

Cyclophosphamide is a prodrug belongs to the nitrogen mustard. It is an alkylating agent, has the potential to cross linkage of DNA (produce highly reactive carbonium ion intermediates that transfer alkyl group to the cellular DNA produce a cytotoxicity activity. After administration of cyclophosphamide (prodrug) converted into an active metabolite phosphamide and acrolein has a cytotoxic activity there by kill the cancer cells. It is the prototype drug of nitrogen mustard group frequently suggested in solid tumor of breast cancers. The most common side effect is alopecia, cytotoxic to the normal healthy cell, the metabolite of the drug acrolein is bladder toxicity and hemorrhagic cystitis (bleeding of bladder) but it can be treated with MESNA which can be externally administered to detoxify the acrolein metabolite of cyclophosphamide.

8.4.2 5- fluorouracil [97]

It is an pyrimidine antagonist. Pyrimidine (thiamine and cytosine) is an DNA genetic material make an bond with purine (adenine, guanine). The primary method of activating 5-FU is the conversion of fluorouridine to fluorouridine monophosphate (FUMP), either directly by orotate phosphoribosyltransferase (OPRT) with phosphoribosyl pyrophosphate as a cofactor, or indirectly via fluorouridine (FUR) through the sequential action of uridine phosphorylase (UrdPase) and uridine kinase (UK). Thymidine phosphorylase (dThdPase), which catalyses the conversion of 5-FU to fluorodeoxyuridine (FUDR), and FUDR's subsequent phosphorylation by thymidine kinase (TK) to FdUMP, make up the other 5-FU activation pathway.

8.4.3 Platinum coordinating complexes [98]

Cisplatin and carboplatin are the platinum coordinating agents. It is a heavy-metal compound with a potent anti-cancer impact. It is a CCNS medication that affects both resting and dividing cells. Because of its strong plasma protein binding and hence concentration in the kidney, testicles, liver, and intestine. It fails to enter the BBB well and passes through the urine slowly. It is administered intravenously. It is an highly reactive paltinium complexes react with DNA by intrastrand and interstand of DNA and cause a DNA damage, hence cytotoxic activity.

8.4.4 Taxanes [99]

Paclitaxel (Taxol), docetaxel (Taxotere), and albumin-bound paclitaxel (Abraxane). Inspite of that paclitaxel is a well-known prototype therapy of taxanes. It is an complex diterpene obtained from the western yew tree.it is administered by intraveneous after injecting through IV it immediately binds to the beta tubulins in microtubule of an breast cancer cell and enhances its polymerization to forms excess abnormal microtubules (it inhibit depolymerization) thereby inhibiting the proliferation of breast cancer cells producing its cytotoxic activity. It is mostly used in metastatic breast cancer and metastatic ovarian cancer.

8.4.5 Anticancer Antibiotics

Antibiotics that fight cancer work directly with DNA. By intercalating between adjacent nucleotide pairs on the same strand of DNA, the drugs doxorubicin, daunorubicin, and dactinomycin bind to DNA and prevent DNA transcription [100]. These are anthracycline antibiotics having an anti-tumour activity. These drug intercalate between DNA strands and blocks DNA as well as RNA synthesis[101,102]. These increase their efficiency and synergetic action it combines with topoisomerase-2 inhibiters like etoposide[103]. Most commonly side effects it that cardiotoxicity causing ECG changes, arrhythmias and hypotension, which seriously cause chronic heart failure leads to fatal, bone marrow depression, alopecia, stomatitis and normal cell toxicity[104].

8.5 Hormone Therapy for Breast Cancer

After biopsy of breast cancer cell it is found that those cancer cell have receptors which has affinity to estrogen and progesterone ultimately made those breast cancer cells to grow[105]. In that situation hormonal therapy is preferred to block estrogen receptors eventually halt the breast cancer cells. Hormonal therapy is performed after only confirmed that ER-receptor positive (ER-estrogen receptor) or PR receptor positive[106p. . Most types of hormone therapy either lower estrogen levels in the body or stop estrogen from helping breast cancer cells grow[107].

8.6 Drugs that block estrogen receptors

8.6.1 Selective estrogen receptor modulators (SERMs)

These medications function by preventing oestrogen from promoting the growth of breast cancer cells

8.6.2 Tamoxifen

Tamoxifen, a selective oestrogen receptor modulator, slows the growth of oestrogen receptor positive cancers and encourages apoptosis. Given that the active metabolite, N-desmethyltamoxifen, has an approximately 2-week half life, it has a lengthy duration of activity [108]. It has a limited therapeutic index because greater doses can cause seizures or difficulties breathing. Administration of tamoxifen is also linked to an increase in uterine cancer incidence. Tamoxifen, which is essential for oestrogen action in breast cancer cells, competitively inhibits oestrogen binding to its receptor [109,110,111].

8.6.3 Selective estrogen receptor degraders (SERDs)

This medication binds to oestrogen receptors. However, SERDs bind to the receptors more firmly and lead to their disintegration [112]. The body as a whole is affected by these medications' anti-estrogen properties. The majority of women who use SERDs have passed menopause. To switch off the ovaries in premenopausal women, they must be administered along with a luteinizing-hormone-releasing hormone (LHRH) agonist [113,114].

8.6.4 Fulvestrant (Faslodex)

Many breast cancer have estrogen receptors and growth of these tumours can be stimulated by estrogen [115]. Fulvestrant is an estrogen receptor antagonist thet binds to the estrogen receptor in a competitive manner with affinity comparable to that of estradiol and downregulation of the ER protein receptor in human breast cancer in a clinical study fulvestrant 250mg is sued in postmenopausal women with primary breast cancer treated with progression free survival 15-22 days prior to the surgery [116,117].

8.6.5 Aromatase inhibitors (AIs)

In women, estrogen is made by the ovaries so after menopausal stage mostover the estrogen is produced by the fat cell by aromatisation of ‘A’ ring of testosterone and androstenedione is the last stage of production of estrogen[119]. The aromatase inhibitors are act by inhibition of aromatase enzyme in these cancer cell in breast thereby halt of aromatisation of testosterone and androstenedione[120].

8.6.6 Letrozole

Adjuvant treatment for postmenopausal women with early breast cancer that has a hormone receptor positive result, progressed or locally advanced breast cancer[121]. Letrozole inhibits the cytochrome P450 enzyme that catalyses the conversion of testosterone to oestrogen by binding to the heme group of aromatase. This results in a considerable drop in plasma oestrogen levels [122,123].

8.6.7 Anastrozole

By blocking aromatase, anastrozole stops the conversion of androstenedione to estrone and testosterone to oestradiol, resulting in markedly lower serum oestradiol concentrations [125]. It enters the GI tract quickly and practically entirely (oral); peak plasma concentrations occur after two hours. may slow down absorption when taken with food[126,127].

8.6.8 Exemestane (aromasin)

Exemestane is a steroidal, irreversible aromatase inhibitor that works as a suicide substrate by covalently attaching to the aromatase enzyme. It has weak androgenic activity, useful in early breast cancer.it is administered orally, also replaced by tamoxifen as adjuvant therapy [128]. This drug is most efficient in lowering the estradiol production and reduce the incidence of breast cancer. Adverse effects is hepatic impairment, hyperlipidaemias, decreasing the bone density occasionally [129].

9 Targeted therapy for women with BRCA gene mutations

9.1 Parp inhibitors

In normal cell proliferation single strand break (SSB) constantly occur which is repaired by basic excision repair mechanism (BER) which is sufficient with HR (Homologues Recombination) it is very much important for the cell repair[130]. In cancerous cell lacks an homologues recombination. PARP (Poly ADP Ribosome Polymerase) is an enzyme used in repairing of the single stand break (SSB). Basic excision repair (BER) is an PARP dependent[131] .Olaparib and niraparib are the PARP inhibitors where mainly considered as against BReast CAncer Susceptibility Protein (BRCA) associated breast and ovarian cancer.

10 Targated drug therapy for HER-1

Geftinib and Erlotinib binds to the Epidermal Growth Factor receptor-1 and halts the growth of cancer cell. Generally this type of medication is used in upregulation of ERFβ-1 receptor or HER-1 receptor positive patient after the biopsy result. Epidermal growth factor (ERF) attach to ERFβ-1 receptor causing an growth of these breast cancer tumour cells, so by blocking these receptors may act as antagonist role and inhibit the growth of breast cancer tumour cells[132].

11 Human epidermal growth receptor -2 inhibitor:

It is also similar to the epidermal growth factor / human epidermal growth receptor -1. Tanstuzumab ia an prototype drug of HER-2 inhibitor. This kind of drug is mostly recommended in patient whose breast tumour has an overexpression of HER-2 receptor [133]. It has long half life about an six hours, so it would be administered weekly at single dose. It is also combined with taxanes or given alone with relapse cases [134].

12 Breast cancer during pregnancy

Having a infant is one of the most joyous moments a person can experience. But for some expecting mothers, they might have to face an even bigger challenge: breast cancer. Breast cancer during pregnancy is rare; however, it can still present itself in some cases and requires special care [135]. Pregnancy is separated into three trimester they are first trimester (0-13 weeks), second trimester (14-26 weeks) and third trimester (27-40 weeks). If the cancer is early detected in pregnancy then the diagnosed whether it is starting (or) metastatic stage [136]. Most of the breast cancer can be detected by normal physical examination like secretion in the nipple, retracted nipple or inverted nipple, lump evolved in the breast are noted [137].

12.1 Diagnosis in first trimester

If breast cancer is discovered during the first trimester, two things should be considered: whether the cancer is in an early or advanced stage. Because a lumpectomy or mastectomy procedure may harm the foetus in the early stages of

detection, it is performed under the supervision of a general anaesthetic specialist [138]. Chemotherapy is generally not recommended during the first trimester because it can cross the placenta and cause foetal abnormalities. In the metastatic stage of detection in pregnant women, the foetus should be aborted, followed by surgery, and adjuvant and neoadjuvant chemotherapy should be administered[139].

12.2 Diagnosis in second and third trimester

Despite the fact that studies show that drugs do not cross the placenta in the second and third trimesters, chemotherapy is not advised[140]. Immediate care should be taken to safeguard the pregnant woman, a possible option is to have a C-section surgical procedure done to deliver the infant [141]. If infant is delivered at 34 weeks, they have the same chances of being healthy as any other infant who didn't arrive too soon [142].

12.3 Breastfeeding during chemotherapy

Breastfeeding should not be recommended during chemotherapy because the drug or its metabolite may enter the breast milk, potentially causing an unhealthy situation in the infant. Alternatively, the child may be fed a synthetic lactose product or may hire a wet nurse. Sometimes, milk is brought from the milk bank [143,144,145].

12.4 Diagnosis of breast cancer in pregnancy

An MRI scan, CT scan, mammography, or biopsy may be undertaken during cancer treatment. While CT scanning and mammography use x-ray radiation to detect tumours in the breast, Precautions should be taken before the diagnosis so that the radiation emitted from the instrument does not reach the infant [64, 70, 74]. During an MRI, a dye known as gadalonium contrast medium may cross the placenta and affect the foetal, such as in the case of rheumatological, inflammatory, or infiltrative skin conditions, as well as stillbirth or neonatal death [146].

13 Conclusion

The study shows breast cancer is a major consecutive life threatening in women , especially it goes severe in pregnancy patient but it is a rare case. There are tremendous complication in safeguard the foetus during chemotherapy. However the chemotherapy therapy should not be recommended during first trimester and abortion should be appreciated. During second and third trimester chemotherapy may be recommended but there is a possibility of foetus abnormalities is expected.

Compliance with ethical standards

Acknowledgments

I would like to acknowledge the Tamil Nadu Chemists and Druggists Educational Trust (TNCDE) and C L Baid Metha College of Pharmacy for the extended support.

Disclosure of conflict of interest

There is no conflict of interest.

Author Contribution

Yuvaraj k had principal responsibility for conception and design of the study and drafting of the manuscript. Dr. P. Muralidaran was responsible for revision of the manuscript for important intellectual content.Francis kevin raj S Govindhan E, Pavithra J, contributed towards reviewing of the literature. All authors agreed on the final version of the manuscript.

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