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BREAST CANCER: COMBATING THE ADVERSE DRUG REACTIONS- A REVIEW

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Abstract:
Breast Cancer is the second most common cancer after skin cancer. It occurs when cells in your breast grow and divide in an uncontrolled way, creating a mass of tissue called a tumor. This review article focuses on different types, causes of breast cancer accompanied with its pathophysiology in brief and the drugs available in the market which are used to combat the adverse effects. The complete cure of cancer being very neglible, drugs available in the market try to reduce the adverse effects of cancer to enhance the longevity of life of the patient. These drugs come with a lot of adverse effects as they tend to act on normal fast proliferating cells and as a result the person not only suffers from cancer, but also a large number of other co-morbidities associated with the drug. This review tries to suggest various medicines and ways which can be employed while administrating the available drugs in order to reduce its side effects and making it more efficacious. These suggested methods to combat the adverse effects are suggestions and might not be effective in all individuals. A doctor's prescription is a must before inculcating these medicines as it may vary from patient to patient depending on their history. These are simply medicine related and improvement in lifestyle related advices, none of them include any invasive or a hospitalized way of treatment. Hence, they can target a large number of audience.

Introduction:

Out of all the diagnosed cancer cases worldwide, breast cancer was found to constitute at least ten percent of them, thereby making it one of the most common malignancy observed in women. According to recent data, breast cancer is the leading cause of death from cancer among women globally. Although, most breast cancers are benign in nature, and can be surgically cured, one in four of all cases grow slowly but have a tendency to metastasize early. (1)

Stages:

Tumor cells of breast cancer arise in the lining or the epithelium of the ducts (approximately 85%) or in the lobules (15%) in the glandular tissue of the breast. During the embryonic stages, the tumor growth is restricted to the duct or lobule where it is asymptomatic and has the least potential to spread to other tissues, which is termed as metastasis. Gradually, these in situ (stage 0) cancers may spread to the surrounding tissues and invade the breast tissue, which is invasive breast cancer. Further, it spreads to the nearby lymph nodes, or regional metastasis. If left untreated, it may even spread to other organs such as the bone, liver, lung and brain, which accounts for its incurability, leading to distant metastasis. (2)High mortality rates in women suffering from breast cancer are attributed to widespread metastasis while early diagnosis assures a higher survival (3)

This review article focuses on the overall study of breast cancer, while highlighting its types, treatment in terms of both, the drugs and the therapies associated with its adverse drug reactions, and a holistic approach to alleviate the same. (4) The prevalence of breast cancer is higher in women as compared to men considered in terms of tumor development. The prevalence in form of statistics could be described as follows: out of the total, 29% of new cancer cases are breast cancer which accounts for 14% of all cancer deaths in the world among women (5). Depending on the development of cancer due to proliferation of cells, there are various stages embarking from early recognition i.e. mere presence to substantial development of the tumor where this growth is evident in the breast tissue. The mechanism of action of proliferation of cells can be described as recreation of cells once the carcinoma has promptly entered in situ and their rapid attack on targeted tissue followed by its spread to the organ causing cancer. Where tumor is concerned, generally an operation is recommended to completely remove the tumor (6) However, it still doesn't guarantee nonrecurrence and hence, a timely follow up is suggested. Different treatments, drugs, therapies and exposure to radiation results in a large number of side effects. (7)

Pathophysiology

The pathophysiology of breast cancer is multifaceted. (8)
It develops as a result of DNA damage and genetic mutations due to exposure to estrogen. It can also be caused due to inheritance of DNA defects or pro-cancerous genes like BRCA1 and BRCA2. As a result, familial history of ovarian or breast cancer predisposes the women to breast cancer. In normal individuals, cells with abnormal DNA or abnormal growth are attacked by the immune system, which is absent in breast cancer resulting in rapid growth and spread of the tumor. (4)
Thyroid cancer and breast cancer seem to have some relationship because survivors of either cancers are at a high risk for developing the other one when compared to the general population. (9)

Classification (cancer/drugs)

Classification of cancer:

Depending upon the breast cancer malignancy, immunohistochemical properties and tumor, they can be classified into 3 types- :

1) Hormone Receptor-positive breast cancer – is most frequently observed and accounts for about 75% of all breast cancers cases. The therapy intends to restrain the synthesis of progesterone and estrogen hormones.

2) HER2-positive breast cancer – Human epidermal development factor receptor-2 positive (HER2-positive) cells produce a high amount of protein known as HER2/neu which accounts for the development of malignancy. On the other hand, HER2-negative cells are the ones that do not over enunciate HER2/neu .

3)Triple negative breast cancer- It can be considered as a subtype of HER-2 negative cancer. The mechanism of action is that malignant cells proliferate in sites where estrogen and progesterone levels are low leading to under expression. It is known to be the most dangerous type and is very difficult to treat as it remains unresponsive to the standard treatment. (7)

Classification of drugs:

1)Systemic therapy for non metastatic breast cancer I)HR+/ERBB-1
a)Tamoxifen

b)Aromatase inhibitors kinase

1) Anastrazole

2) Exemestane

3)Leterozole

c)Atezolizumab

II)chemotherapy Regimen Selection for ERBB2 gene

1 docetaxel/cyclophosphamide

2 adriamycin/cyclophosphamide

3 cyclophosphamide/ methotrexate/5-fluorouracil III) Triple negative subtype- neo adjuvant chemotherapy : adriamycin/cyclophosphamide followed by paclitaxel and docetaxel/carboplatin, phenytoin, thiazolidinedions

IV) Epidermal growth factor receptor

a) monoclonal antibody- Paclitaxel/trastuzumab,

II)Immunotherapy:

- Elimination Phase
- Equilibrium phase
- Escape phase

III)Monoclonal antibodies:

1)Trastuzumab

2)pertuzumab

3)Lapatinib

4)Neratinib

5)Afatinib

6)Gefitinib

IV)Systemic therapy for metastatic breast cancer :

A)Abemaciclib

B)Palbociclib

C)Ribociclib

(10)

Systemic therapy for non metastatic Breast cancer is determined by the following subtypes:

1. Patients with hormone receptor–positive tumors receive endocrine therapy, and a minority receive chemotherapy as well.

2.Patients with ERBB2-positive tumors receive ERBB2-targeted antibody or small molecule inhibitor therapy combined with chemotherapy.

3.Patients with triple-negative tumors receive chemotherapy only.

4. Local therapy for most patients with nonmetastatic breast cancer comprises surgical resection, with consideration of postoperative radiation if lumpectomy is performed. Metastatic breast cancer is treated according to subtype, with goals of prolonging life and alleviating symptoms.

The table below summarizes the **essential characteristics of drugs**. :

Drug name	Mechanism of action	Positive action on patient	Adverse effects	Combating adverse effects
Tamoxifen	Selective estrogen receptor modulator that competitively inhibits the binding of estrogen to estrogen receptor. (11)	Suspension of cell cycle in the G1 phase of tumor cells. Subsequent delay of cell proliferation. Directly induces apoptosis (programme d cell death). (12)	Menopausal symptoms: Hot flashes Atrophic vaginitis Irregular menses Ocular toxicity Thromboembolic events Thrombo-cytopenia or leukopenia Gynecologic complications Low grade Endometrial cancer Endometrial hyperplasia Ovarian cysts (13)	A combination treatment of tamoxifen-risperidone can be employed in breast cancer patients which is a conceivable resolution of tamoxifeninduced side effects without interfering with the efficacy of tamoxifen against breast cancer. (14)
Anastrazole	It inhibits the conversion of adrenal androgens such	Indicated in the treatment of advanced breast	Hot Flashes Muscle/Joint pain Stomach upset	Combination therapy with Fulvestrant might be more

	as testosterone to estrogen in the peripheral as well as tumour tissues. As the growth of many breast cancers is stimulated or maintained by the presence of estrogen, anastrozole helps treat these cancers by reducing the levels of circulating estrogens. (14)	cancer in post-menopausal women experiencing disease progression and are unresponsive to tamoxifen therapy.	Decreased energy Mood disturbances Sore throat Hypertension Depression Nausea Vomiting Rash Osteoporosis (Weak bones) Fractures Back pain Insomnia (Trouble sleeping) Headache Peripheral oedema and lymphedema (fluid build-up) Dyspnoeal (difficulty breathing) Increased cough (15)	effective than anastrozole alone in patients with HR+ metastatic breast cancer. Vitamin D and Calcium supplements have to be prescribed in case of deficiency. For nausea or vomiting - a 5HT-3 receptor antagonist such as Ondansetron may be used. Occasional headaches - Mild pain relief medications such as Paracetamol (16)
Exemestane	Irreversible steroidal aromatase inhibitor. It forms covalent bonds with the substrate binding site of the enzyme leading to irreversible aromatase inactivation, i.e., "suicidal inhibition." (17)	Potent inhibitor with a higher aromatase affinity when compared to other analogs. (18) It reduces serum estradiol levels. (19)	Decreased bone mineral density (BMD) with increased risk of bone fractures Joint pain and stiffness Carpal tunnel syndrome Menopausal symptoms Arthralgia Altered lipid metabolism. (14,20,21)	When compared with tamoxifen, exemestane causes fewer thromboembolic and gynecological events. Nausea and vomiting - dopamine D2receptor antagonist (Domperidone) and a 5HT-3 receptor antagonist such as Ondansetron. (22) Calcium and Vitamin D

				supplements have to be taken as a prophylactic measure as Exemestane may cause Osteoporosis. (23)
Letrozole	Highly specific, nonsteroidal, third-generation aromatase inhibitor with similar mechanism as that of Anastrozole.	Plasma levels of estrone and estradiol were remarkably reduced in post-menopausal women with breast cancer. (24)	Hot flushes Nausea Headache Hair thinning Arthralgia, Myalgia Arthritis (25)	Nausea and vomiting - dopamine D2receptor antagonist (Domperidone) and a 5HT-3 receptor antagonist such as Ondansetron. Calcium and Vitamin D supplements have to be taken as a prophylactic measure as exemestane may cause Osteoporosis. (26)
Transtuzumab	Trastuzumab inhibits constitutive HER2 cleavage shedding assisted by metallo- proteases. The ability of trastuzumab to inhibit HER2 cleavage depends upon the clinical anticancer activity of the multifunctional HER2-targeting antibody. Trastuzumab also is involved in other biological	The beneficial effects were greatest in patients with the greatest degree of HER2 protein overexpressi on. The magnitude of observed effects was greatest with paclitaxel plus trastuzumab. (28)	Fever Chills Pain Asthenia Nausea Vomiting Increased cough Diarrhea Headache Dyspnea Infection Rhinitis Insomnia Cardiac dysfunction Congestive heart failure (29)	For nausea and vomiting- Common medications for nausea include ondansetron (Zofran) and prochlorperazine maleate (Compazine). It is best to take these medications about an hour before eatin g. This will help you maximize how much you can eat and allow you to enjoy your meal more and use

	functions such as sensitizing HER2-overexpressing cancer cells to chemotherapy by downregulating HER2 expression. (27)			ginger and peppermint. For asthenia- Methyl-prednisolone; Amphetamines like dextro-amphetamine, methylphenidate and mazindol. For rash- For mild symptoms of an allergic reaction, keep receiving Herceptin. (30)
Pertuzumab	A humanised monoclonal antibody that binds to the extracellular domain II of HER2. Inhibits the formation of both heterodimers and homodimers in the presence of an HER2 ligand. Inhibiting ligand dependen t HER2–HER3 dimerization. (31)	Pertuzumab is useful in both the metastatic and the neoadjuv ant settings. The combination therapy of pertuzumab and trastuzumab was well tolerated in patients with metastatic HER2-positive breast cancer who had previously experienced disease progression during trastuzumab therapy. (32)	Diarrhoea Nausea Vomiting Fatigue Asthenia Back pain Minimal cardiac dysfunction Rashes	For diarrhea- Loperamide For nausea and vomiting- ondansetron (Zofran) ,prochlorperazin e maleate (Compazine). It is best to take these medications about an hour before eating. This will help you maximize how much you can eat and allow you to enjoy your meal more and use ginger and peppermint. For asthenia- Methyl-prednisolone, Amphetamines like dextro-amphetamine, methylphenidate and mazindol

Lapatinib	Tyrosine kinase inhibitor, which inhibits both the HER1 and HER2 receptors . It reversibly attaches to and competes with ATP for binding to the intracellular (ATP) binding site of the receptor. (33)	In second line treatment in combination with letrozole. Combining lapatinib and trastuzumab in HER2 over expressing cell lines, has additive or synergistic effects. (34)	Most common: Dyspnoea Pleural effusion Fatal adverse effects: Headache Diarrhoea Rash Cold symptoms Gastrointestinal symptoms Fatigue Nausea Anorexia Vomiting Back pain (35)	Headache- Over-the-counter pain relieversacetaminophen (Tylenol) and ibuprofen (Advil, Motrin) steroid antibiotics. Prescription narcotic pain relievers, like codeine; Tricyclic antidepressants Triptan medication-sumatriptan For diarrhea-Loperamide. Steroid medications, especially for headaches caused by cancer that spreads to the brain. (36)
Neratinib	It inhibits the phosphorylation of ErbB gene, by covalently combining with cysteine residues. It also causes decreased phosphorylated retinoblastoma protein which is responsible for major G1 checkpoint, blocking S phase entry and cell growth in tumour cells. (37)	Down-regulate HER 2 expression. It can inhibit ATP-binding cassette transporter and thereafter reverse multidrug resistance of cancer cells. (37)	Most common: Diarrhoea Nausea Abdominal pain Vomiting Fatigue Stomach-ache Headache Rash Decreased appetite Muscle spasms Dizziness (22)	For diarrhea-Loperamide For nausea and vomiting- ondansetron and prochlorperazine maleate. It is best to take these medications about an hour before eatin g. This will help you maximize how much you can eat and allow you to enjoy your meal more and use ginger and peppermint.

				(38)

Afatinib	Potent, irreversible, highly selective inhibitor of EGFR/HER1, HER2 and HER4 tyrosine kinase activity which is crucial for cell proliferation and inhibition of apoptosis. Their suppression is critical in controlling tumor growth. (39)	Promising clinical activity in HER2-positive breast cancer patients who had progressed following treatment with trastuzumab. (40)	Cutaneous (rash, acne, and dry skin) Gastrointestinal toxicities (diarrhea, mucositis, nausea and vomiting).	For nausea and vomiting- ondansetron (Zofran) and prochlorperazine maleate (Compazine)Take these medications about an hour before eatin g. Use ginger and peppermint also. For diarrhea- Loperamide For stomatitis- Alleviated after 2 weeks of therapy with Aznol mouthwash, a chamomile extract with antiinflammatory effects, and Hangeshashinto, a traditional herbal (Kampo) medicine. (40)
Gefitinib	EGFR tyrosine kinase inhibitor. It works by binding to the intracellular enzyme (tyrosine kinase) of the EGFR to directly block signals turned on by triggers outside or inside the cell. (41)	Promising antitumor activity was observed. All adverse effects are dose dependent and reversible.	Skin rash Diarrhoea Asthenia Erythema Dyspepsia (42)	For dyspepsia- By consuming antacids, H2- receptor antagonists, proton pump inhibitors, prokinetics and antibiotics (42)
Atezolizumab	It binds to the programmed cell death ligand-1 and blocks its interactions with	Improved survival rate for the chemotherap y and	Pyrexia Fatigue Nausea Diarrhea Asthenia Pruritus	Nausea and vomiting - Domperidone and Ondansetron

	the programmed cell death-1 and CD80 receptors. (43)	immunothera py combination without disease progression.	Rash Decreased appetite Vomiting, Headache Hypothyroidism Arthralgia Hyperhidrosis Myalgia Dizziness Hyponatremia Neutropenia Pain Anemia Pneumonitis Adrenal insufficiency Lichen planus Fatigue Hyperglycemia Hypertension Hypokalemia White blood cell count decreases Pulmonary hypertension (can be fatal). (43)	High blood pressure - Adjust the dose of the anti hypertensive medicine Diarrhoea and inflamed bowel - Eat less fibre, avoid raw fruits, fruit juice, cereals and vegetables, and drink plenty of liquid to replace the fluid lost. Skin changes, such as dryness, itching and rashes.- Wear a high factor sun block if you're going out in the sun. Joint or back pain- Painkillers such as Paracetamol may be of use
Abemaciclib	Inhibitor of CDK4 and CDK6 activity, which inhibits phosphorylation of retinoblastoma tumor suppressor protein. (44)	Prevents progression through the cell cycle.	Diarrhoea Neutropenia Nausea Abdominal pain Infections Fatigue	Diarrhoea and inflamed bowel - Eat less fibre, avoid raw fruits, fruit juice, cereals and vegetables, and drink plenty of liquid to replace the fluid lost. For neutropenia- cefepime For fatigue- Eszopiclone (Lunesta) Ramelteon (Rozerem) Zolpidem (Ambien)

				(38)

Ribociclib	Selectively inhibits cyclindependent kinase 4 (CDK4) and 6 (CDK6), causing inhibition of retinoblastoma (Rb) protein phosphorylation early in the G1 phase leading to cell cycle arrest	Prolongation of progression-free survival and high rates of overall response with the addition of ribociclib for the first line treatment in post menopausal women, with HR-positive, HER2 negative advanced breast cancer. (45)	Myelo-suppression, Elevated bp among patients in the ribociclib group	Combination of Ribociclib and Letrozole improves survival in Advanced Breast Cancer and is better tolerated. The drug may also elevate serum cholesterol levels and the dose of hypolipidemic medication has to be adequately adjusted. Anti hypertensive medicine has to be adequately adjusted. (46)
Doxorubicin	Doxorubicin stabilizes the topoisomerase II complex after it has broken the DNA chain for replication, preventing the DNA double helix from being released and thereby inhibiting the process of replication. (47)	Doxorubicin interacts with DNA by intercalation and blocking of macromolec ular biosynthesis	Hair loss Bone marrow suppression Vomiting Rash Inflammation of the mouth Anaphylaxis Heart damage Tissue damage at the site of injection Treatmentrelated leukemia Red discoloration of the urine for a few days Dilated cardiomyopathy Congestive heart failure, Enlargement of all four cardiac chambers	Dexrazoxane decreases the risk of doxorubicin's cardiotoxicity Nausea- Anti Nausea like ondansetron , promethazine in combination SPF 50 For protection from sun Nutritional medicines like becadexami n , uprise D3 cholecalciferol tablets.

			Systolic and diastolic dysfunction Typhlitis- an acute lifethreatening inflammation of the bowel Loss of skin pigmentation (48)	
Cyclophosphomide	The metabolite phosphoramide is formed in cells that have low levels of Aldehyde dehydrogenase (ALDH). Phosphoramide mustard forms DNA crosslinks both between and within DNA strands at guanine N-7 positions. (49)	This is irreversible and leads to cell apoptosis.	Low WBC count, loss of appetite, vomiting, hair loss and bleeding from the bladder. Increased future risk of cancer, infertility, allergic reactions and pulmonary fibrosis.	Nausea and vomiting- drug therapy (Domperidone and Ondansetron). Changes in diet such as eating several small meals or limiting activity may help lessen some of these effects. (38)
Paclitaxel	Binds to the beta-tubulin subunits of microtubules. Defects in mitotic spindle assembly, chromosome segregation and cell division occur upon administration. It stabilizes the microtubule polymer and protects it from	The ability of paclitaxel to inhibit spindle function is generally attributed to its suppression of microtubule dynamics. It inhibits the progression of mitosis	hair loss, bone marrow suppression, numbness, allergic reactions, muscle pains, and diarrhea. Other serious side effects include heart problems, increased risk of infection and lung inflammation.	Dexamethasone is given prior to paclitaxel infusion to mitigate some of the side effects. To reduce nausea, (ondansetron, promethazine) and eat small, frequent meals.

	disassembly. Chromosomes are unable to achieve a metaphase spindle configuration. (50)	and triggers apoptosis. (48)		Antidiarrheal- Loperamide Mouth sores- betadine Gargles Weight gain - anorexigenic drugs like megestrol and Marinol (43)
Carboplatin	Occur via aquation and activation	Carboplatin interferes with DNA duplication and growth of cancer cells, which eventually are destroyed	Low blood cell levels, nausea, and electrolyte problems. allergic reactions and increased future risk of another cancer Myelosuppressi ve effect causing the blood cell and platelet output of bone marrow in the body to decrease. This decrease in white blood cells (neutropenia) can cause complications. The most notable complication of neutropenia is increased	Neutropenia- Filgrastim drug Infections- essential antibiotics Kidney and liver problemsNSAIDS, octreotide, midodrine Loss of hearing and tinnitus- dose change requirement Nausea and vomitingondansetron promethazine (43)
			probability of infection by opportunistic organisms. (49)	

Thiazolidinedio ne	Thiazolidinedio nes activate peroxisome proliferatoractivated receptors, a group of nuclear receptors, specific for PPARγ (PPARgamma, PPARG). (51)	Antineoplastic effects in the cancer cell including apoptosis, growth arrest, and differentiati on. (52)	Oedema (main side effect) Thiazolidinedio nes reduces bone mineral density and increases the risk of fractures in women due to biasing the differentiation of bone marrow stromal cells away from osteoblast differentiation and toward adipocyte formation. It increases the chance of serious infection with the SARS-CoV-2 virus, which causes COVID-19. (51)	Thiazolidinedio nes should be prescribed with both caution and patient warnings about the potential for water retention/weigh t gain, especially in patients with decreased ventricular function. (51)

-HR+/ERBB- Subtype ***1 Tamoxifen-***

Tamoxifen is administered in both pre and postmenopausal women. It is taken orally and is effective. Patients who were treated with tamoxifen had 36% lower risk of developing meningioma than those who were not. (13)

Tamoxifen is administered to patients as a trans isomer (citrate salt), because it has a higher affinity for estrogen receptor (ER) than the cis isomer. (53)

Its estrogen-antagonist activity in breast tissue accounts for its ability to suspend tumor growth. The major metabolites seen in humans are N-desmethyl tamoxifen and trans4hydroxytamoxifen.

Tamoxifen inhibits the expression of estrogen-regulated genes, including growth factors and angiogenic factors secreted by the tumor which may stimulate growth by autocrine or paracrine mechanisms. (54)

The following medications are to be avoided when tamoxifen is being administered:

1. Antidepressants such as Paroxetine, Bupriopion & Duloxetine
2. Cardiac medicines such a Quinidine and Ticlopidine
3. Estradiol, Warfarin, Colchicine

Tamoxifen is contraindicated in Hypersensitivity, Pregnancy, Undiagnosed vaginal bleeding and history of thromboembolism.

2 Aromatase inhibitors (anastrozole, exemestane, and letrozole)- It decreases circulating estrogen levels by inhibiting conversion of androgens to estrogen and are effective only in postmenopausal women.

i ***Anastrazole*** - It is a competitive, selective, non-steroidal aromatase inhibitor used as an adjuvant during the treatment of hormone receptor-positive breast cancer in postmenopausal women. It is taken orally and is effective. It has a longer duration of action which indicates once daily dosing. Absorption is comparatively rapid and hepatic metabolism occurs via oxidation and glucuronidation to a number of inactive metabolites, which include hydroxyanastrozole (both free and glucuronidated) and anastrozole glucuronide. (15) Fulvestrant binds and accelerates degradation of estrogen receptors. (16) Contraindications:

1)In osteoporosis: Anastrozole reduces oestrogen levels in the body, which can cause bones to become brittle. Bone mineral density levels of the patient need to be checked

2)In hyperlipidemia: It has potential to elevate serum cholesterol levels. Therefore cholesterol levels of the patient have to be monitor and the dose of the hypolipidemic medication has to be adequately adjusted. (38)

ii ***Exemestane*** -

Its route of administration is subcutaneous or oral. An oral dose of exemestane is rapidly absorbed and metabolism occurs through CYP3A4.(55) The major metabolite in the plasma is 17-hydroxyexemestane. Impaired renal and hepatic function, lead to reduced metabolism, and elevated plasma levels. (56–58)

It may also elevate blood pressure levels (hypertension). The dose of the anti hypertensive medicine used should be adequately adjusted. Exemestane may also block peripheral estrogen production, which impacts vaginal symptoms and sexual dysfunction. Women should be counseled on methods that may help alleviate these symptoms. For example, the use of vaginal lubricants, moisturizers, and vaginal massage with coconut oil are some examples of treatments that may benefit women who experience vaginal dryness or pain. Combination therapy with exemestane and celecoxib has also shown promising efficacy in advanced breast cancer. (59)

A combination therapy of Goserelin and exemestane is a highly efficacious and welltolerated regimen in premenopausal women with hormone-responsive locally advanced and metastatic breast cancer. (60)

iii)***Letrozole*** - It is administered orally once daily. It is rapidly and almost completely absorbed from the gastrointestinal tract. It is metabolised via the cytochrome P450 enzymes (CYP3A4 and CYP2A6) to a pharmacologically inactive metabolite (4,4'methanolbisbenzonitrile) followed by renal excretion. Concurrent administration of tamoxifen and letrozole reduced the plasma levels of letrozole when compared with that of letrozole administered alone. (61)

Letrozole is contraindicated in pre- menstrual, pregnant and lactating women. Letrozole reduces oestrogen levels in the body, which can cause bones to become brittle. The drug also has a potential to increase blood pressure levels, therefore blood pressure levels have to be monitored and the dose of anti hypertensive medicine has to be adequately adjusted. (26)

iv) ***Atezolizumab*** - It is an Fc-engineered, non-glycosylated, humanized, monoclonal immunoglobulin-G1 (IgG1) antibody. (43)

Adverse effects like skin rashes, and other hypersensitivity reactions subside with time. Low thyroid hormone levels can be overcome by monitoring the levels of hormone and providing supplements if needed.

-Chemotherapy Regimen Selection for ERBB2 Subtypes

1 Adriamycin/Cyclophosphamide

2 Cyclophosphamide/Methotrexate/5-Fluorouracil :

Combination therapy with methotrexate + sulfasalazine+ hydroxychloroquine (triple therapy) or methotrexate + most biologic Disease modifying antirheumatic drugs (DMARDS) or tofacitinib were similarly effective in controlling disease activity and generally well tolerated

in methotrexate-naïve patients or after an inadequate response to methotrexate.

Methotrexate + some biologic DMARDs were superior to methotrexate in preventing joint damage in methotrexate-naïve patients.

(43)

-Triple negative subtype

Neoadjuvant chemotherapy employed- The combination therapy used is: adriamycin/cyclophosphamide followed by paclitaxel and docetaxel/carboplatin, phenytoin and thiazolidinediones.

1)Doxorubicin- Brand name: Adriamycin

Doxorubicin is a chemotherapy medication which treats cancer. It is often used together with other chemotherapy agents. The drug dexrazoxane may be used to decrease the risk of doxorubicin's cardiotoxicity in certain cases. Chemotherapy can cause reactivation of hepatitis B.

Doxorubicin belongs to the anthracycline class of antitumor antibiotic of medications. It works in part by interfering with the DNA function.

It may also increase quinone type free radical production, contributing to its cytotoxicity. Do not take aspirin or products containing aspirin unless your doctor permits this. 2)Do not receive any kind of vaccination without your doctor's approval while taking Doxorubicin

Contraindicated in Pregnancy, congestive heart failure. (47)

2)Cyclophosphamide:

Cyclophosphamide (CP), also known as cytophosphane is a medication used as chemotherapy and to suppress the immune system. It is administered orally or intravenously. Its metabolism is mainly through liver. It's Excretion is performed by kidney. The main effect of cyclophosphamide is due to its metabolite phosphoramide mustard.

Cyclophosphamide is converted in liver by mixed-function oxidase enzymes (cytochrome P450 system) to active metabolites. The main active metabolite is 4hydroxycyclophosphamide, which exists in equilibrium with its tautomer, aldophosphamide. (49)

Side effects /ADR:

Profound gonadotoxicity, Easy bruising/bleeding, joint pain, mouth sores, slowhealing of existing wounds, unusual decrease in the amount of urine or unusual tiredness or weakness.

Cardiotoxicity (dose dependent), syndrome of inappropriate antidiuretic hormone secretion (SIADH), potentially fatal hyponatremia, cystitis, Infertility- dose dependent and reversible bladder bleeding.

Risks of hemorrhagic cystitis can be minimized with adequate fluid intake, avoidance of nighttime dosage and mesna (sodium 2-mercaptoethane sulfonate), a sulfhydryl donor which binds and detoxifies acrolein. Intermittent dosing of cyclophosphamide decreases cumulative drug dose, reduces bladder exposure to acrolein and has equal efficacy to daily treatment in the management of lupus nephritis.

Lower back pain, headache, joint and muscle pain - Treated with paracetamol or NSAIDs.

Diarrhea - Sufficient fluid therapy to restore fluid and electrolyte balance. Intermittent dosing of cyclophosphamide decreases cumulative drug dose, reduces bladder exposure to acrolein and has equal efficacy to daily treatment in the management of lupus nephritis (Causes kidney inflammation and may lead to blood in the urine, protein in the urine, high blood pressure, impaired kidney function or even kidney failure.) Avoid any immunization or vaccine while on Cyclophosphamide therapy as body's immune system is compromised and the vaccine may not function. Contraindications: teratogenic and therefore contraindicated in pregnant women.

(62)

3) Paclitaxel (PTX) - Brand name - Taxol

It is administered intravenously. It's Excretion is performed via urine and faeces.

Side effects /ADR:

Avoid sun exposure. Wear SPF 15 (or higher) sunblock and protective clothing. Drink at least two to three quarts of fluid every 24 hours, unless you are instructed otherwise.

Alternate compounds and related compounds :

Albumin-bound paclitaxel is an alternative formulation where paclitaxel is bound to albumin nanoparticles. (43)

Synthetic approaches to paclitaxel production led to the development of another molecule docetaxel, that has similar set of clinical uses as Paclitaxel.

In general, drinking alcoholic beverages should be kept to a minimum or avoided completely. You should discuss this with your doctor. (62)

4) Carboplatin

It is administered intravenously. It's Excretion is performed by kidney.

Side effects/ADR:

Side effects generally occur

Use during pregnancy may result in harm to the baby. Carboplatin is in the platinum-based antineoplastic family of medications and works by interfering with duplication of DNA. Relative to cisplatin, the greatest benefit of carboplatin is its reduced side effects, particularly the elimination of nephrotoxic effects. (43)

5)Thiazolidinediones:

The thiazolidinediones (TZD or glitazones) after the prototypical drug ciglitazone, are a class of heterocyclic compounds.

Immunotherapy as an Option for Cancer Treatment The three theories: Immunosurveillance, Immunoevasion and Immunoediting have been of keen interest in cancer immunity for a long time. (63)

Immunoediting theory is based on three E's: Elimination, Equilibrium and Escape. The host immune system shapes tumor fate in three phases via the activation of innate and adaptive immune mechanisms.

(64)

Elimination phase- this phase is characterized by successful recognition and destruction of cancer cells by body's immune system. The success of the immune system to eliminate tumor cells depends on the ability of the antigen to trigger immune response, or immunogenicity. Sporadic tumor cells that manage to survive immune destruction may then enter equilibrium phase.

Equilibrium phase- Immune system controls the tumor growth but is unable to eliminate it completely.

Escape phase- It represents the final phase of the process where immunologically sculpted tumor begins to grow progressively and is clinically apparent establishing an immunosuppressant tumor microenvironment. The tumor may overcome the entire immune defence and enter the escape phase where it progresses and metastasizes. Emergence of clinical symptoms of cancer is seen in this stage.

Monoclonal Antibodies: The initial cancer immunotherapy treatments used humanized monoclonal antibodies that bind and neutralize a targeted altered molecule expressed by cancer cells, on which their survival and multiplication depends. Trastuzumab was the first antibody for the treatment of metastatic breast cancer patients with HER2 (Receptor tyrosineprotein kinase ERBB2, CD340) overexpression and/or gene amplification. Following Trastuzumab other anti-HER2 monoclonal antibodies including lapatinib, Neratinib, Gefitinib, Afatinib used either as monotherapy or in combination with conventional treatments . Although monoclonal antibodies have improved the outcome of cancer patients, just adequate response rates and resistance development have lowered the success of the treatment. Newer approaches which include antibody-drug conjugates (ADC) such as adotrastuzumab emtansine is the most promising strategy for breast cancer patients . (51,65) The approved humanized monoclonal antibodies with their adverse drug reactions seen with them are the following:

1 Trastuzumab –

Trastuzumab, sold under the brand name Herceptin among others, is a monoclonal antibody. It falls under the category of monoclonal antibody/ whole antibody. It is administered intravenously and subcutaneously .It can be given only on prescription basis. It's metabolism occurs by reticuloendothelial system. Monotherapy with trastuzumab is active and well tolerated as a first-line treatment of women with metastatic breast cancer with HER2 3+ overexpression. (14)

Preclinical studies have shown that trastuzumab alone or in combination with paclitaxel or carboplatin remarkably inhibits the growth of breast tumor-derived cell lines that overexpress
the HER2 gene product. (49) Two significant trials were performed to evaluate trastuzumab
efficacy and safety:
(1) trastuzumab in combination with chemotherapy as first-line therapy (2) trastuzumab as
a single agent in second- and third-line chemotherapy.
(66)
In vivo, trastuzumab induces antibody-dependent cellular cytotoxicity.

The risk of cardiomyopathy is increased when trastuzumab is combined with anthracycline chemotherapy (which itself is associated with cardiac toxicity)
(67,68)

2 Pertuzumab –

Pertuzumab monotherapy leads to disease progression. Although pertuzumab has some activity in patients with HER2-positive breast cancer that progressed during therapy with trastuzumab, the combined use of pertuzumab and trastuzumab provided better results than monotherapy. (32)
It is more potent as compared to Trastuzumab.
(29,69,70)

3 Lapatinib –

It is administered orally. It has the ability to overcome trastuzumab resistance. Lapatinib ditosylate monohydrate targets the C-terminus tyrosine kinase domain of both the HER2 and EGFR receptors. This inhibits both phosphorylation and activation of the downstream cascades resulting in cell cycle arrest and apoptosis .Lapatinib is considered a potent inhibitor .It can be pretreated with prior anthracycline and taxane. (6,33,35,36,71)

4 Neratinib –

Several studies have shown that neratinib provides a benefit in survival outcome. Combination therapy with other anticancer agents is beneficial. (29,37,70,72)

5. Afatinib -

A clinical study was conducted to assess the efficacy and safety of afatinib monotherapy in patients with HER2-positive metastatic breast cancer.
A/E profile was manageable. (39)
Mechanism of action - Afatinib has been investigated in multiple Phase I clinical trials. These studies have revealed a manageable side effect profile both when used as monotherapy and in combination with other chemotherapeutic drugs (including cisplatin/paclitaxel, cisplatin/5fluorouracil, and docetaxel). Its pharmacokinetic profile revealed oral bioavailability and moderately fast absorption. Afatinib is rapidly distributed in the tissues with moderate-to-high clearance. Elimination majorly occurred via faeces. (7,40,52,73,74)

6 Gefitinib:

It was generally well tolerated and it had low activity in patients with advanced breast cancer. (41,42)

Systemic Therapy for Metastatic Breast Cancer

In metastatic HR+/ERBB2− breast cancer, early treatment should be employed with first or second line endocrine therapy based, cyclin dependent kinase (CDK) 4/6 inhibitor, such as abemaciclib, palbociclib, or

ribociclib. After resistance develops to the available hormonal options, patients transition to treatment with chemotherapy.

In ERBB2+ metastatic breast cancer, standard first-line therapy includes a taxane plus trastuzumab and pertuzumab, and the antibody-drug conjugate trastuzumab emastine is used as second-line therapy.

A recent phase 3 trial nab-paclitaxel plus the programmed death ligand

1 (PD-LI) inhibitor atezolizumab (3)

1 ***)Abemaciclib***

Three major clinical trials, namely MONARCH 1, 2, and 3, established the efficacy and safety of abemaciclib for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer bemaciclib may be a suitable option because of its continuous dosing and ability to be used as monotherapy.

(44,75)

2)Palbociclib

It is an orally available cyclin-dependent kinase inhibitor that is used in combination with aromatase inhibitors in the treatment of postmenopausal women with metastatic breast cancer.

MOA- CDK4 and 6 play a key role in the regulation of cell cycle progression.

3)Ribociclib

It is administered along with an endocrine therapy and resulted in significantly longer overall survival than endocrine therapy alone in patients with hormone-receptor–positive, HER2-negative advanced breast cancer. (45,46,52)

Conclusion

In conclusion, this review summarizes the types of breast cancer and, its mechanism of action and the positive effect it has on the patient. The main focus of this review is combating adverse effects using a more holistic approach rather than invasive techniques. Along with this, different measures are taken for different drugs depending on their target site. The above given medications are generic suggestions but its effect may vary from patient to patient and one should only opt for these medications based on the patient's medical history and sensitivity towards these drugs.

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