

CHEMOTHERAPY AND HORMONE THERAPY FOR BREAST CANCER AND COMPLICATIONS

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Abstract

Breast cancer is second leading cause of death in women. Treatment modalities for breast cancer optimized according to stage at which the cancer is diagnosed. Chemotherapy, hormone therapy and targeted therapies are used for the treatment of advanced stages of disease. The aim of therapy different like to enhancing the curative rate in adjuvant therapy, reduce symptoms or improve quality of life in metastatic diseases, reduce the chances of the cancer coming Back. The complications of therapy including mental function; cardiovascular functions; neuromusculoskeletal and movement related functions and structures functions of hematological immunological and respiratory system etc. The benefits of chemotherapy are limited and relative compared to the risk factors. Chemotherapeutic agents use in treatment of breast cancer such as taxanes (docetaxel and paclitaxel), tamoxifen, vincristine, cyclophosphamide, trastuzumab etc.

Keyword: breast cancer, hormone therapy, targeted therapy, chemotherapy, adjuvant therapy.

Introduction

In 2018, over 627,000 women died from breast cancer – that is near by 15% of all cancer deaths in women¹. In India breast cancer ranked number one expected to be diagnosed 25.8 per 100,000 women and mortality 12.7 per 100,000 women². Breast cancer is a new lump or mass, it involves regional lymph nodes and associated with typical features of tissues. The treatment of breast cancer is depends on stage of cancer which consist surgery, radiation, chemotherapy and hormone therapy, target therapy. When micrometastasis occurs, the disease is cured by chemotherapy and hormone therapy along with surgery. Sometimes doctors prefer to give patients chemotherapy before surgeries that shrink the tumor, which reduce the surgery to be invasive. Following breast cancer treatment, women develop acute and late complications that affect functions and quality of life.

Chemotherapy for breast cancer

Chemotherapy uses anticancer drugs that kill or disable cancer cells in the breast or other places. Anticancer drugs may be given intravenously (injected into vein) or by oral route (mouth)³, by a port-a-catch (inserted into skin of the chest).

Chemotherapy may be recommended:

After surgery (adjuvant chemotherapy): Adjuvant chemotherapy is given after surgery used to kill any cancer cells that are left or spread. It increase the cure rate and reduces the chances of cancer come back. **Before surgery (neoadjuvant chemotherapy):** Chemotherapy given

before surgery to shrink the tumor so it can be removed with less extensive surgery.

Advanced breast cancer: Chemotherapy is used for main treatment in advanced breast cancer women whose cancer is spread to outside breast.

Breast cancer chemotherapy drugs

Treatment by chemotherapy of breast carcinoma can be determined by organized screening and identification of the ailment⁴, and tumor stage. The final decision for choice of treatment by outweighs the benefits and risks.

Chemotherapeutic agents used for breast cancer treatment:

- Alkylating agent: cyclophosphamide (Cytoxan)
- Anthracyclines: doxorubicin (Adriamycin) and epirubicin (ellence)
- Platinum agents: cisplatin (platinol), carboplatin (paraplatin)
- Taxanes: paclitaxel (taxol) and docetaxel (taxotere)
- Hormone and antagonist: tamoxifen (nolvadex), letrozole (femara) and anastrozole (arimidex)
- Trastuzumab (Herceptin)
- Lapatinib
- Vincristine (oncovin)
- 5-Fluorouracil (5-FU)
- Methotrexate
- Capecitabine (xeloda)

Hormone therapy

Tamoxifen, selective estrogen receptor modulator that bind to estrogen receptor and blocks angiogenesis, lowers

insulin-like growth factor 1 and transforming growth factor production⁵. Tamoxifen is most commonly used following surgery/ or radiation for the treatment of invasive breast cancer in both men and women. Radio labeled Tamoxifen 20 mg dose oral administration as standard for breast cancer therapy⁶. Response rate of tamoxifen therapy is 50-70%, progression time is ~6 months and response duration is 12-18 months⁷.

Aromatase inhibitors are chief estrogen source in post menopausal breast cancer treatment. Aromatase inhibitors work by inhibiting the action of enzyme aromatase which convert androgens into estrogens and testosterone to estrogen⁴. Most commonly used aromatase inhibitors are exemestane (aromasin), letrozole (femara) and anastrozole (arimidex).

Chemotherapeutic agents

The platinum compounds like cisplatin and carboplatin are used employed as monotherapy or in combination regimen in metastatic breast cancer (MBC). Platinum compounds are DNA-binding alkylating agents causes DNA damage cell lose the ability of cell repair, the cell undergoes apoptotic cell death⁸.

Anthracyclines: Doxorubicin and epirubicin are used in the combination regimen (i.e.AC, FAC, TAC) as chemotherapeutic agents in this class to treat breast cancer. They inhibit cancer by different way like free radical generation which destroy nucleic acid, inhibit topoisomerase II enzyme, DNA intercalation, inhibit HIF-1 transcriptional factor from binding to DNA in cells and inhibit tumor growth in human⁹.

Taxane (paclitaxel and docetaxel) regimens are most commonly used systemic therapy in adjuvant therapy of breast cancer. Taxanes causes mitotic arrest in G₂ and M phase by inhibition of microtubules dynamics (i.e. promote polymerization and inhibit depolymerisation), leading to cell death¹⁰.

Alkylating agent (Cyclophosphamide) used in metastatic breast cancer which avert DNA replication and cell division, regardless of cell cycle phase. Cyclophosphamide is a pro drug which convert into active metabolites 4-hydroxycyclophosphamide, acrolein, aldophosphamide, and phosphoramide mustard by hepatic intracellular enzymes. The drug is used in combination regime of anthracycline or CMF in adjuvant therapy of breast cancer.

Trastuzumab is a humanized recombinant monoclonal antibody, works against the HER₂-receptor protein on breast cancer cells. Trastuzumab is clinically safe and effective, response rates ranged 12%-23% for single agent trastuzumab and 25%-62% for trastuzumab plus

chemotherapy for metastatic breast cancer. It is administered i.v dose 4mg/kg followed by weekly doses 2mg/kg¹¹.

Capecitabine is an oral anti-metabolite pro drug of fluoropyrimidine that convert into 5-FU by thymidine phosphorylase enzyme. 5FU inhibits thymidylate synthase resulting inhibition of DNA synthesis. Response rate improves when Capecitabine is used in combination therapy with paclitaxel, docetaxel.

Complication of chemotherapy

Cardiovascular toxicity

Cardiovascular toxicity is a short-long term complication of chemotherapy of breast cancer. Anthracyclines, trastuzumab, fluorouracil, taxanes therapy, damage the myocardium, resulting cardiomyopathy. Cardiotoxicity, is defined as absence of symptoms with ventricular ejection-fraction reduction $\leq 10\%$ to $< 55\%$ ¹². Chemotherapy of breast cancer patients having pre-existing cardiac pathology, those who are older, left breast irradiation therapy operative, are mostly develop cardiovascular complication.

Fatigue

Fatigue is common side effect of chemotherapy of breast cancer patients or survivors¹³. Fatigue is hard to define it is, sleeping more, as feeling tired, weak, exhausted, lazy, not wanting to do normal activities. Main causes of breast cancer related fatigue are depression, pain, decreased activities, incomplete sleep, and illness. Chemotherapy related fatigue improves after therapy is completed, but some level of fatigue may persist for months or years. 14-96% of patients undergoing cancer treatment and in 19-82% of patients during post-treatment¹⁴ are reported experience fatigue due to chemotherapy.

Myelosuppression

Myelosuppression, or bone marrow suppression, decrease ability of the bone marrow to produce blood cells, resulting in a reduction of red blood cells (erythrocytes), white blood cells (leukocytes) and platelets (thrombocytes), is most common dose limiting side effect of chemotherapy¹⁵. Decrease in

healthy red blood cells (below 37% to 47% or hemoglobin below 12-16g/dl) to carry adequate oxygen to your body's tissues is called anemia, cause dyspnea and fatigue. A reduced level of neutrophils (below 2500-8000 per mm³) is called neutropenia, lead to increase the chances of infection. A reduction of platelets (below 150,000 platelets per mm³) is called thrombocytopenia (CIT), which causes gastrointestinal bleeding, nose bleeding,

hematuria, petechiae, increase clotting time or unable to clot.

Neuropathy

Chemotherapy induced Peripheral neuropathy depend on the type and dosage of drugs received. When small fiber damage (results painful paresthesias and dysesthesias), and large fiber damage (result raised vibration and touch thresholds). There are three main substance groups that are involved in development of CIPN: the platinum-based antineoplastics (particularly oxaliplatin and cisplatin), the vinca alkaloids (particularly vincristine and vinblastine), the taxanes (paclitaxel, docetaxel). Patients shown to have Sensory disturbances, muscle weakness, pain, numbness, tingling, autonomic disturbance, decreased postural stability, myalgias. Cisplatin-induced neuropathy is variable, with some patients reporting symptoms after the first dose, and others after 12 cycles of therapy, after cumulative doses above 350 mg/m², with approximately 92% of patients developing neurotoxic symptoms¹⁶

Cognitive dysfunction

Adjuvant chemotherapy treatment for breast cancer survivors reports cognitive dysfunction. Study by Arash Asher et al. 16% to 75% of patients with breast cancer experience cognitive impairment during chemotherapy, compared with 4% to 11% of healthy controls¹⁷. Although proposed mechanisms have been suggested to explain cognitive dysfunction includes, anemia, direct neurotoxic effects of therapy (eg, inhibition of hippocampal neurogenesis), genetic predisposition, oxidative damage, and immune dysregulation, and also have depression stress, pain, anxiety, and fatigue.

Hair loss

Chemotherapeutic agents are powerful medications that attack rapidly growing cells of body along with cancer cells. Chemotherapy of breast cancer survivors may cause hair loss all over body — not only scalp, but also eyelash, eyebrow, armpit, pubic and hairs on all body parts.

Weight gain

Weight gain is a common side effect of chemotherapy, affecting up to ~60% of women¹⁸. Chemotherapy cause weight gain by different ways such as nausea i.e. improved by eating, decrease metabolism, less physical activity, body hold excess body fluid, and Triggering intense food cravings.

Other side effect

Here are some other common side effect of chemotherapy such as fever, nausea and vomiting, anemia, appetite change, constipation, diarrhea, mouth and throat sores,

nail weakness, risk of infection, sleep disorder, fertility problems. Side effect of tamoxifen includes uterine hyperplasia and small chances of pulmonary emboli and deep vein thromboses¹⁹.

CONCLUSION

In choosing chemotherapy of breast cancer, it should be clearly recognize the purpose of the treatment, whether it is used for breast conservation as preoperative therapy, or cure of disease as postoperative adjuvant therapy or to increase quality of life in metastatic breast cancer. Trastuzumab is advised in patients have high risk with HER2/ neu positive breast cancer. Aromatase inhibitors are used rather than tamoxifen as adjuvant therapy in post menopausal women. Implementation of chemotherapy of breast cancer require to weigh benefits and risks, management of adverse drug reactions, after treatment specially myelosuppression, hair loss, nausea and vomiting, neuropathy.

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