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REVIEW OF CHEMOTHERAPY IN BREAST CANCER: EVOLVING PARADIGMS AND FUTURE DIRECTIONS

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ABSTRACT

Breast cancer remains the most common malignancy among women worldwide and a leading cause of cancer-related mortality.[9] [2]. This review provides a comprehensive overview of breast cancer epidemiology, risk factors, molecular classifications, pathogenesis, diagnostic advances, and therapeutic strategies.[2][5][3]Key risk factors include genetic mutations like BRCA1/2, hormonal influences, obesity, and lifestyle elements, with early detection via mammography and biomarkers improving outcomes.[2] [10] [8]Therapeutic approaches encompass surgery, radiation, chemotherapy, hormone therapy for ER-positive tumors, and targeted agents like trastuzumab for HER2-positive cases, alongside emerging options for resistant subtypes.[5] [3] Personalized medicine and multidisciplinary care optimize survival, though challenges persist in aggressive forms like triple-negative breast cancer.[2] [3]Ongoing research into novel therapies and prevention underscores the need for continued innovation.[5] [3]

KEYWORDS:- 1. Breast cancer, 2. Epidemiology, 3. Molecular classification 4. Personalized medicine 5. Targeted therapy, 6. Triple negative breast cancer.

INTRODUCTION

Chemotherapy remains a cornerstone of systemic treatment for breast cancer,both in the curative (early-stage) and palliative (metastatic) settings. Its role has evolved from a one-size-fits-all approach to a more nuanced strategy integrated with the tumor's molecular subtype, genomic risk profiling, and patient-specific factors [4, 11]. Cytotoxic agents work by disrupting cellular division and inducing apoptosis in rapidly dividing cancer cells. The

advent of molecular classification (Luminal A/B, HER2-enriched, Triple-Negative Breast Cancer [TNBC]) has been instrumental in defining which patients derive the most benefit from chemotherapy, sparing those with highly endocrine-sensitive, low-risk disease [4, 6]. Despite significant advances in targeted and immune therapies, chemotherapy retains critical importance, particularly for TNBC and in overcoming or delaying resistance in hormone receptor-positive and HER2-positive cancers [6, 11]. This review details the contemporary use of chemotherapy in adjuvant and metastatic settings, highlights novel chemotherapeutic agents, and outlines future directions.

Adjuvant Therapy for Early-Stage Breast Cancer

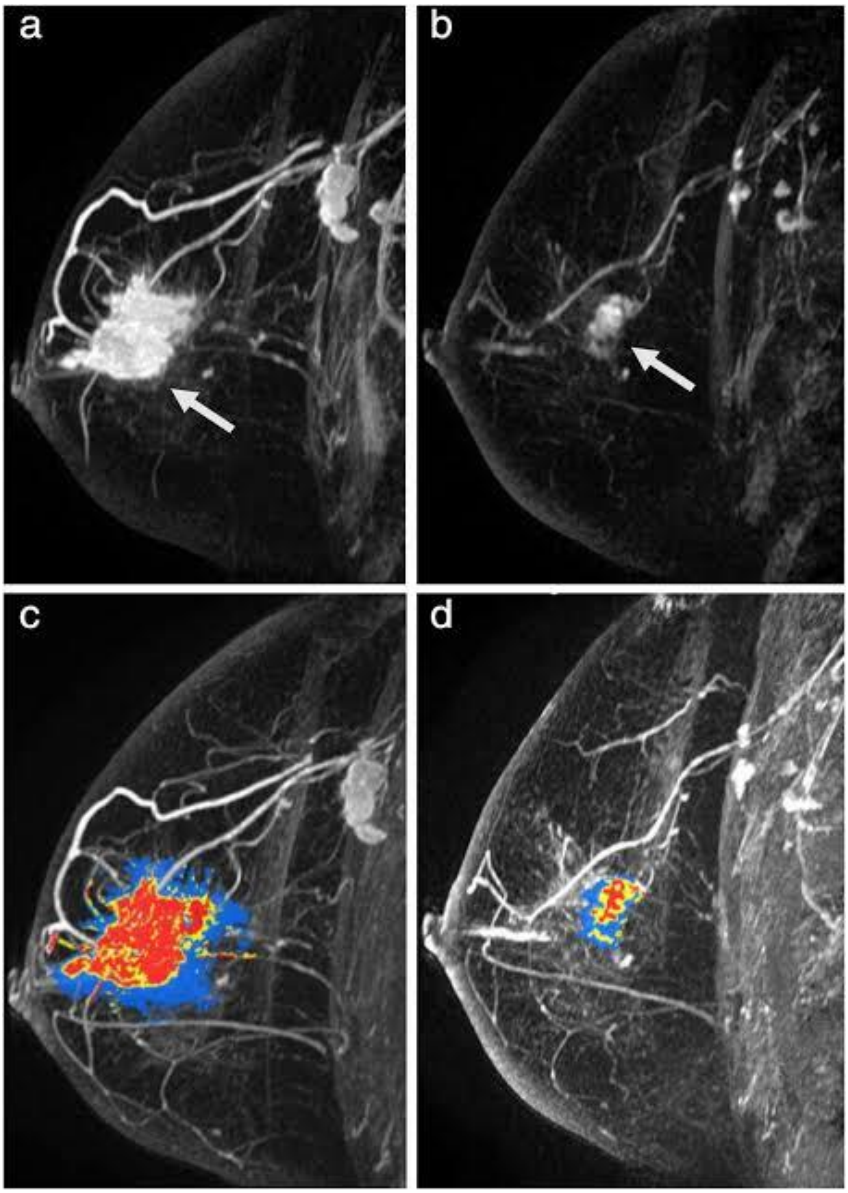
The goal of adjuvant chemotherapy is to eradicate micrometastatic disease following surgery,thereby reducing the risk of recurrence and improving overall survival. Regimen selection is guided by disease stage, tumor biology, and genomic assays.

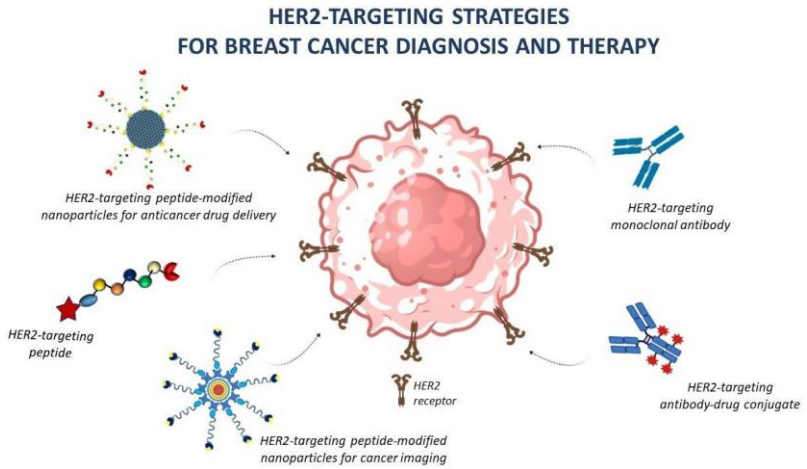
Standard Regimens: Anthracycline- and taxane-based combinations represent the historical backbone. Common sequences include dose-dense doxorubicin/cyclophosphamide followed by paclitaxel (AC-T) or docetaxel/doxorubicin/cyclophosphamide (TAC) [11, 16]. These regimens have demonstrated clear survival benefits in high-risk patients.

Genomic Guidance: For hormone receptor-positive (HR+), HER2-negative disease, multigene assays like the 21-gene recurrence score (Oncotype DX) and the 70-gene signature (MammaPrint) are pivotal. They identify patients with such a low risk of recurrence that chemotherapy can be safely omitted, favoring endocrine therapy alone [4, 16]. For example, the TAILORx and RxPONDER trials refined the use of chemotherapy in pre- and postmenopausal women based on recurrence score and nodal status.

TNBC and HER2-Positive Disease: These subtypes derive substantial benefit from adjuvant chemotherapy. For TNBC, dose-dense anthracycline/taxane regimens are standard. The addition of capecitabine or platinum agents (carboplatin) in high-risk settings (e.g., residual disease post-neoadjuvant therapy) is supported by trials like CREATE-X and BrightTNess, which showed improved outcomes [6, 11]. For HER2-positive disease, chemotherapy (e.g., paclitaxel) is combined with dual HER2-targeted therapy (trastuzumab + pertuzumab) as per the APHINITY trial paradigm [11]. ***Neoadjuvant Chemotherapy:*** Administering chemotherapy before surgery is standard for locally advanced or inflammatory breast cancer and is increasingly used in operable high-risk subtypes (HER2+, TNBC). It allows for tumor downstaging and provides critical in vivo response data. The achievement of a pathological complete response (pCR) is a powerful prognostic surrogate, particularly in HER2+ and

TNBC, and guides post-surgical therapy decisions [6, 11]. [23]





Chemotherapy of Metastatic Breast Cancer (MBC)

In the metastatic

setting,chemotherapy is primarily palliative, aiming to control disease, alleviate symptoms, and prolong survival while maintaining quality of life. The choice and sequence depend on tumor subtype, prior therapies, toxicity, and patient preference. [22]

HR+/HER2- MBC: Chemotherapy is typically reserved for use after endocrine therapy and CDK4/6 inhibitors have been exhausted or for visceral crisis requiring a rapid response. Single-agent sequential therapy is preferred over combination chemotherapy to minimize cumulative toxicity [11, 14].

HER2+ MBC: Taxanes (docetaxel, paclitaxel, nab-paclitaxel) remain the preferred chemotherapy partners for first-line trastuzumab/pertuzumab. In later lines, chemotherapy is combined with other HER2-targeted agents like trastuzumab emtansine (T-DM1) or trastuzumab deruxtecan (T-DXd), which are themselves antibody-drug conjugates (ADCs) containing potent chemotherapeutic payloads [11].

TNBC MBC: Chemotherapy is a mainstay due to the lack of targetable receptors. Preferred first-line agents include taxanes or anthracyclines (if not used in early-stage disease). For PD-L1-positive TNBC, chemotherapy (nab-paclitaxel) combined with immune checkpoint inhibitors (pembrolizumab, atezolizumab) has become a new standard based on KEYNOTE-355 and Impassion130 trials, significantly improving progression-free and overall survival [6, 11].

Treatment Principles: Sequential single-agent therapy is standard. Common active agents include taxanes (paclitaxel, docetaxel, nab-paclitaxel), anthracyclines (doxorubicin, liposomal doxorubicin), antimetabolites (capecitabine, gemcitabine), and microtubule inhibitors (eribulin, vinorelbine). The choice is influenced by prior adjuvant therapy, treatment-free interval, and organ function [14].

Other Chemotherapeutic Agents with Activity in MBC

Beyond classical cytotoxics,several newer agents and drug classes have expanded the chemotherapeutic arsenal.

1. Eribulin Mesylate: A non-taxane microtubule dynamics inhibitor approved for pretreated MBC. It demonstrates survival benefits in anthracycline- and taxane-refractory disease and is noted for potential effects on tumor vasculature and epithelial-mesenchymal transition [14].

2. Platinum Salts (Carboplatin, Cisplatin): Particularly active in TNBC, especially in tumors with homologous recombination deficiency (e.g., BRCA1/2 mutations). Their use is well-

established in the neoadjuvant setting and is increasingly common in selected metastatic cases [6].

3. Antibody-Drug Conjugates (ADCs): These represent a paradigm shift, combining monoclonal antibody specificity with potent cytotoxic payloads.

Sacituzumab Govitecan (SG): A Trop-2-directed ADC coupled with SN-38 (a topoisomerase I inhibitor). Approved for pretreated HR+/HER2- and TNBC, it has shown superior survival over single-agent chemotherapy in the TROPiCS-02 and ASCENT trials, respectively [11, 19].

· Trastuzumab Deruxtecan (T-DXd): A HER2-directed ADC with a topoisomerase I inhibitor payload. It has revolutionized treatment for HER2-low (a new category defined as IHC 1+ or 2+/ISH-negative) MBC, showing unprecedented efficacy in the DESTINY-Breast04 trial, and remains highly active in later-line HER2-positive disease [11, 20].

4. Novel Formulations: Liposomal doxorubicin offers a favourable toxicity profile with reduced cardiotoxicity and is valuable for patients with cardiac risk factors or prior anthracycline exposure.

5. Emerging Agents (2023-2025): Research continues into optimizing chemotherapy delivery and overcoming resistance. Next-generation ADCs with novel targets (e.g., HER3, FRα, B7-H4) and different payloads (e.g., novel topoisomerase inhibitors, immunotoxins) are in advanced clinical development. Furthermore, strategies to modulate the tumor microenvironment to enhance chemotherapy efficacy, such as combining it with anti-angiogenic agents or novel immune modulators, are being actively investigated [21].

CONCLUSIONS

Chemotherapy remains an indispensable component of the breast cancer treatment continuum. Its application has been refined through precision medicine, with molecular subtypes and genomic tools guiding its use in early-stage disease to maximize benefit and minimize overtreatment. In the metastatic setting, sequential single-agent chemotherapy, often strategically combined with targeted or immunotherapy, provides vital disease control. The landscape is being transformed by the advent of ADCs like T-DXd and SG, which effectively blur the lines between targeted therapy and chemotherapy, offering enhanced efficacy with improved therapeutic indices. Future directions focus on further personalization through biomarkers (e.g., homologous recombination deficiency for platinum), developing smarter drug delivery systems, and rational combinations to overcome resistance. Continued innovation in chemotherapeutic agents and their integration into multimodality strategies is

essential to improving outcomes, particularly for patients with aggressive and treatment-resistant breast cancer subtypes

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