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Chemotherapeutic Drugs Used Across Various Stages of Breast Cancer: A Scoping Review

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Abstract: ***Background**: Breast cancer develops when the cells in the breast begin to grow uncontrollably. These cancer cells have the ability to spread from breast lobules and milk ducts to various parts of the body through blood and lymph vessels, leading to metastasis. It has various stages i. e.0, I, II, III and IV which can be further re - classified as early, locally advanced and advanced based on the size of the tumor, spread of cancerous cells to lymph nodes and presence/absence of metastasis. Identification of the type of cancer cells (estrogen receptors positive, progesterone receptors positive, human epidermal factor 2 positive and triple - negative) help ascertain the most effective treatment pathways. Surgery, radiotherapy, chemotherapy, hormone therapy, targeted therapy, and immunotherapy are some of the therapeutic options for breast cancer patients. Chemotherapy involves administering drugs to cancer cells to inhibit their growth. Through this scoping review, we aim to develop a better overview of all the chemotherapeutic drugs in use around the world at varying stages of breast cancer. **Method**: Thorough search was conducted on databases such as PubMed, Cochrane central and Google scholar. Apart from screening of the studies based on predefined inclusion and exclusion criteria, data extraction and assessment of methodological quality was carried out independently by two reviewers, using a standard checklist. **Results**: Through this scoping review, we have enlisted various chemotherapeutic drugs according to their usage in different stages of breast cancer. It includes a detailed analysis of the geographical settings of the included studies, the interventions used, and the endpoints used across the included studies. **Discussion**: Numerous research on chemotherapeutic drugs have been undertaken, conveying information on efficacy, chemo - resistance, toxicity, drug - drug interactions, adverse events, and the usage of one or a combination of drugs. However, data on an aggregated list of breast cancer chemo drugs is lacking and it is highly imperative to fill up the existing research gap. While the key findings delve into the pros and cons of various chemotherapeutic regimens, strict stage - based categorization of drugs still remains a challenge owing to the nuanced and ever - evolving essence of oncology. The consolidation accomplished in this study is nevertheless, expected to be of significant advantage for the expertise of clinicians and researchers in the field.*

Keywords: Breast Cancer, Chemotherapeutic Drugs, Scoping Review, Treatment Stages, Global Analysis

List of Abbreviations

4AC4 cycles of Doxorubicin and Cyclophosphamide
A Doxorubicin Hydrochloride (Adriamycin)
ABC/MBC Advanced/Metastatic Breast Cancer
AC Doxorubicin and Cyclophosphamide
ACT Adjuvant Chemotherapy
AC - T sequential Anthracycline - Cyclophosphamide and Taxane
ATMAtaxia Telangiectasia Mutated
BCS Breast - Conserving Surgery
BRCA1 Breast Cancer gene 1
BRCA2BReastCAncer gene 2
BRIP1BRCA1 Interacting Protein
C Cyclophosphamide
CAF, Cyclophosphamide, Doxorubicin (Adriamycin) and fluorouracil
CDH1Cadherin 1
CHEK2Checkpoint Kinase 2
CMF Cyclophosphamide, Methotrexate and 5 - Fluorouracil
CONSORT Consolidated Standards of Reporting Trials
DFS Disease Free Survival
E Epirubicin Hydrochloride
EBC Early Breast Cancer
EBCTCGEarly Breast Cancer Trialists' Collaborative Group
E - CMF Epirubicin, Cyclophosphamide, Methotrexate and 5 - Fluorouracil
F Fluorouracil
FEC, Fluorouracil, Epirubicin and Cyclophosphamide
M Methotrexate
MRIMagnetic Resonance Imaging

mTNBC metastatic Triple Negative Breast Cancer
NACT Neo - adjuvant Chemotherapy
NCCN National Comprehensive Cancer Network
ORR Overall Response Rate
OS Overall Survival
PALB2Partner And Localizer Of BRCA2
pCR Pathological Complete Response
PFS Progression Free Survival
PRISMA Preferred Reporting Items for Systematic Reviews and Meta - Analyses
PTENPhosphatase AndTensin Homolog
QoL Quality of Life
STK11Serine/Threonine Kinase 11
T Paclitaxel (Taxol)
TAC Docetaxel (Taxotere), Doxorubicin (Adriamycin) and Cyclophosphamide
TNBC Triple Negative Breast Cancer
TP53Tumor Protein P53
TTP Time To Progression
WHO World Health Organization

1. Background

The Disease

Breast cancer is the type of cancer which occurs when the breast cells start growing uncontrollably. A breast consists of 3 major parts i. e. lobules, milk ducts and connective tissue. It can further spread through blood vessels and lymph vessels to other parts of the body which is termed as metastasis (1) . Individuals with personal and/or family history of breast cancer have a higher risk of developing the disease at some point in their life (2) . Mutations in some of the rare, but highly penetrant genes such as BRCA1, BRCA2, PTEN, TP53, CDH1 and STK11 are responsible for up to 25% of the total hereditary cases. Further 2 - 3% of the cancers are attributable to other rare genes with moderate penetrance such as CHEK2, BRIP1, ATM, and PALB2 (3).

Stages of breast cancer

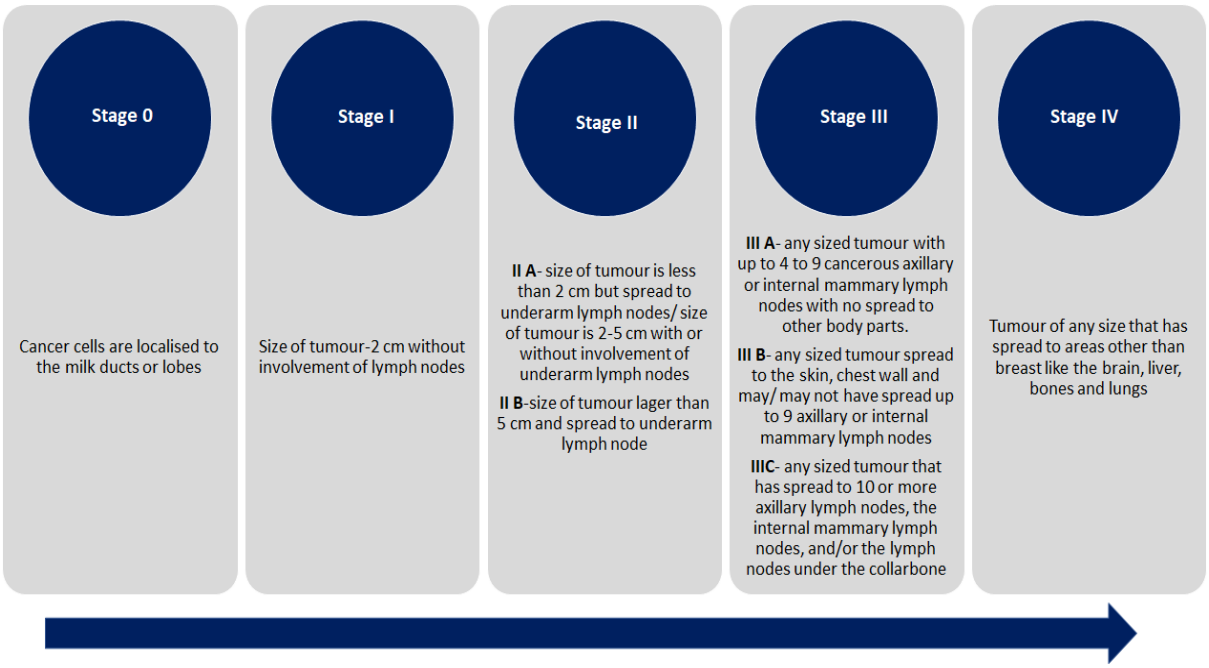

Figure 1: Various stages of breast cancer

Cancer is always referred to by the stage in which an individual has been diagnosed even if the cancer later spreads and progresses to higher stages (4) .

1) Stage 0

It is also known as non - invasive or in situ carcinoma and the presence of tumour in this case is restricted to the milk ducts or gland without invading the surrounding tissues of the breast. This is not cancer but has the possibility of developing into one (4, 5) .

2) Stage I

- Stage IA: In this stage the tumour is either 2 cm or less without spreading to the axillary lymph nodes (6) .
- Stage IB: Small groups of cancer cells exist in the lymph nodes and the tumour is either not present at all or if present, is smaller than 2 cm (6) .

3) Stage II

- Stage IIA: In this stage ither the tumour is less than 2 cm in size but has spread to 1 - 3 lymph nodes or is sized between 2 - 5 cm but without spread to any lymph nodes (6) .
- Stage IIB: The tumour is sized anywhere between 2 - 5 cm with extent of spread to 1–3 axillary lymph nodes, or is larger than 5 cm but without spread to any lymph nodes (6) .

4) Stage III

- Stage IIIA: A tumour of any size which has spread to 4 - 9 axillary or internal mammary lymph nodes without spreading to other parts of the body. A tumour larger than 5 cm and extent of spread upto 1 - 3 axillary lymph nodes also comes under this stage (7) .
- Stage IIIB: When a tumour invades the chest wall or skin and may/may not have spread up to nine axillary or internal mammary lymph nodes. There is no spread of the tumour to other parts of the body (7) .
- Stage IIIC: A tumour of any size that is found in 10 or more axillary lymph nodes, the internal mammary nodes, and/or the lymph nodes near the collarbone. There is no spread of the tumour to other parts of the body (7) .

5) Stage IV

In this case the tumour can be of any size, and its cancer cells have spread to nearby and distant lymph nodes as well as distant organs primarily the brain, bones, lungs and liver (7) .

Diagnostic tests

Most commonly used diagnostic tests for breast cancer areimaging tests i. e., ultrasound, diagnostic mammography, magnetic resonance imaging (MRI) and biopsy. Various genomic tests help further to determine tumour characteristics and provide specialized treatments (8) .

Risk factors for breast cancer

a) **Non - modifiable factors**: Age, family history of breast/ovarian cancer, genetic predisposition, previous radiation therapy treatment exposure, personal history of breast/ovarian cancer, early menstruation, and late menopause (2) .
b) **Modifiable factors**: Time of first pregnancy, weight, hormone replacement therapy, breastfeeding, low levels of physical activity, alcohol, socio - economic factors (2, 9) .

Treatment

There are different types of treatment options available for patients with breast cancer. Standard treatment used are surgery, radiation therapy, hormone therapy, targeted therapy, immunotherapy and chemotherapy.

Chemotherapy

Chemotherapy is a cancer treatment that involves administering chemicals to cancer cells in order to limit their growth, either by killing them or preventing them from growing. Chemotherapeutic drugs enter the bloodstream and can reach cancer cells all throughout the body when taken by mouth or injected into a vein or muscle (systemic chemotherapy) (13, 14).

List of chemotherapeutic drugs:

- **Taxanes** - paclitaxel, paclitaxel albumin - stabilized nanoparticle formulation, docetaxel
- **Anti - metabolites** - capecitabine, 5 - fluorouracil, methotrexate sodium
- **Anthracyclines** - doxorubicin hydrochloride, epirubicin hydrochloride, gemcitabine hydrochloride
- **Microtubule inhibitors** - eribulinmesylate, ixabepilone, vinblastine sulfate, vincristine
- **Alkylating agents** - thiotepa, cyclophosphamide, cisplatin
- **Commonly used drugs in India:** paclitaxel, carboplatin, doxorubicin, cyclophosphamide, 5 - fluorouracil
- **Drug Combinations Used in Breast Cancer:** AC, ACT, CAF, CMF, FEC, TAC (13)

Burden

Global scenario

Breast cancer is one of the leading causes of death among women worldwide and is also responsible for highest number of disease adjusted life years (DALYs) when compared to other types of cancers (10) . According to WHO, 2.3 million women were diagnosed with breast cancer whereas approximately 0.7 million died owing to this in 2020 alone (10) . Soaring incidence rates are seen in Australia/New Zealand, Europe, and North America, with the highest rates in Europe and Australia. Contrastingly, rates of incidence in Sub - Saharan African regions, particularly Eastern, Middle Africa, and South Central Asia, were notably lower (11) . The importance of chemotherapy as a cancer treatment regimen lies in its versatile utilization. Apart from being the primary treatment of advanced or metastasized stages where surgery is not possible, it is also used before surgery as neo - adjuvant therapy to shrink the size of tumour and post - surgery to reduce risk of recurrence (12). In England, around 34% of patients diagnosed with breast cancer underwent curative or palliative chemotherapy as part of their primary cancer treatment in 2013 - 2014 (13) . About 17% of US - based breast cancer patients received chemotherapy in stage 2, 62% in stage 3 and 66% in stage 4, as per a American Cancer Society (ACS) report 2019 - 21 (14) .

Indian scenario

In India, 27.7 % of all newly detected cancers in women in 2018 were breast cancer, making it the most common cancers among women. While an estimated 1, 62, 468 women were newly diagnosed with breast cancer, 87090 women died of breast cancer in 2018, the second highest number in the world for that year (15) .

Rationale

Historically, the incidence of breast cancer has been reportedly higher among the developed countries but with the progressing years, the developing world is also witnessing a sharp rise in such cases leading to high morbidity and mortality. There are numerous studies that inform us about the efficacy, chemoresistance, toxicity, drug - drug interactions, adverse events and use of one or a combination of few chemotherapeutic drugs. However, there is limited systematic data that gives comprehensive details on all the existing and reported stage - specific

chemotherapeutic drugs being used as a part of treatment regimen for breast cancer.

Aim of the study
The aim of this review is to attain a better understanding of all the chemotherapeutic drugs being used globally across various stages of breast cancer.

Objectives
To undertake a systematically searched scoping review on the chemotherapeutic drugs used for the treatment of breast cancer across all its stages.

2. Methods

We referred to the general guidelines for conducting a systematic review as suggested in the CochraneRevman Handbook for systematic reviews. The detailed elaboration of steps for primary screening, inclusion criteria, keyword selections, data extraction and assessment of bias that was taken for the review have been mentioned in the subsequent sections. Figure 3 represents the flow chart for the study.

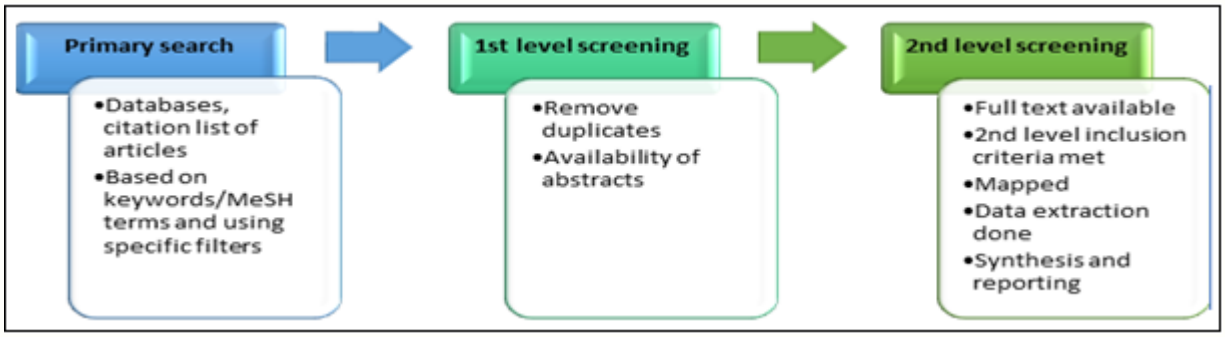

Figure 2: Flow chart for the review of literature

Eligibility Criteria
We included study designs like Randomised controlled trials and Meta - analysis. Preference was given to meta - analysis studies.

Other specifications:

Inclusion criteria
- Papers published only in the English language were included
- Place of study: Anywhere in the world
- Studies conducted on chemotherapeutic drugs till date

Exclusion criteria
- Studies done on breast cancer in men
- Studies on women who have had complete mastectomy

Information Sources
Based on the inclusion criteria, search was done on the following search engines and other sources:
a) Electronic databases: freely accessible and available electronic databases like PubMed, Cochrane central, Google scholaretc.
b) A detailed examination of cross references and publications was performed to identify additional sources of information.

Search Strategy
For selection of studies, a set of keywords, relevant to the primary study question were used for searching the databases. These were "chemotherapy, ", "breast cancer, " and "women, ". The complete search strategywhich was developed using these keywords and the search builder used was ((((((((((CTX) OR (Anti - neoplasticdrugs)) OR (Pharmacotherapies)) OR (Pharmacotherapy)) OR (Chemotherapies)) OR (Chemotherapy)) OR (therapies, drug)) OR (Drug Therapies)) OR (Therapy, drug)) AND (((Breast Neoplasm) OR (Breast Tumor) OR (Mammary Cancer) OR (Malignant Tumor of Breast) OR (Mammary Carcinoma, Human) OR (Mammary Neoplasms) OR (Breast Carcinoma In Situ) OR (Carcinoma of breast) OR (malignant neoplasm of breast) OR (lobular carcinoma) OR (ductal carcinoma in situ))) AND (((females) OR (ladies) OR (women)))).

3. Data Collection and Analysis

Selection of studies
The studies included in the review were selected as per a structured search strategy. Two reviewers, independently, selected the studies to be considered in the review. Screening was done independently following which the abstract review was carried out for the selected studies. This review was conducted independently and then the final list of citations was prepared. Further, all the selected articles were reviewed by both the reviewers independently. All discrepancies wereresolved through discussion, involving a third member of the review team. In case any study wasexcluded from further analysis, appropriate justification was provided for doing so.

Data extraction and management
Data was extracted from the selected studies by two authors independently and all the relevant information was tabulated and stored in Microsoft excel. Themajor summary elements included in the review weretype of publication, year of study, first author, study design and methodology, sample size, study population, study duration, stage of cancer at baseline, inclusion/exclusion criteria, chemotherapeutic drug used, other key findings and conflict of interest. Each team member's data extraction was reviewed by the other team member to assure accuracy. Differences in data extraction were resolved through reference to original articles and discussion, to establish consensus. All discrepancies were

resolved with discussion, involving a third member of the review team if found necessary. Standard systematic review guidelines were used for data analysis.

Methodological quality assessment of included studies

The methods were applied independently by two authors. For assessing the quality of selected studies, a thorough review to identify the external and internal validity of included studies was performed. Further, we used PRISMA checklist for meta - analysis and systematic reviews and CONSORT guidelines for randomized control trials to finally list down studies for in - depth review based on mutual agreement between the primary reviewers.

4. Results

Selection of studies

PubMed was primarily used for online record searching which yielded 480 papers to be evaluated for this review. No duplicates were found. Post screening of 480 studies, 255 were excluded based on information gathered from their titles. Further, the abstracts of thus selected studies (n=225) were assessed.80 studies were excluded from these owing to their non - alignment with our study objectives. A total of 75 studies had their full text reviewed. Of these, 31 meta - analyses were included in this scoping review. Since these were later found to be sufficiently informative and meta - analysis is acknowledged for providing highest level of evidence, we did not search for other types of studies stated in our protocol.6 studies were additionally identified through cross - referencing out of which 2 were included in final data synthesis.

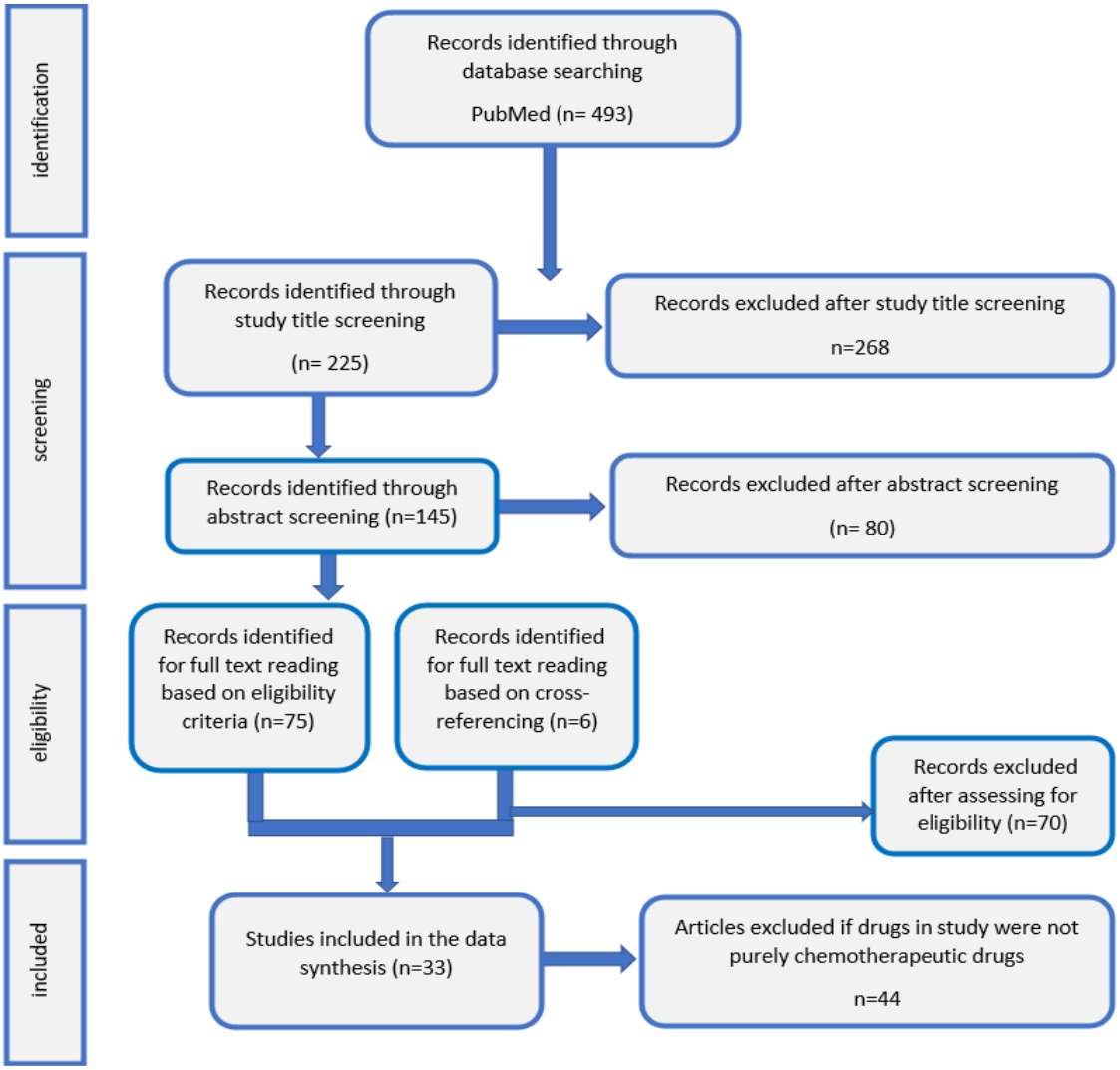

Figure 3: Prisma flow chart

Geographical settings of included studies

Majority (19/33: 57.6%) of the studies were carried out in high income countriesnamely UK, USA, Italy, Netherlands and Australia while 12 (12/33: 36.4%) of them were from China (High Middle Income Country) and 2 (2/33: 6.1%) from Iran (Middle income country) (Figure 4). Age of the participants in the included studies varied widely which ranged from 15 - 85 years.

Out of the 33 studies, 17 studies were based on drugs used in early breast cancer while 16 others focused on drugs used in metastatic or advanced breast cancer patients. Considerable

variation in the size of the studies was observed. The number of included patients ranged from 500 to 100, 000 with the total count of 2, 74, 134 patients.

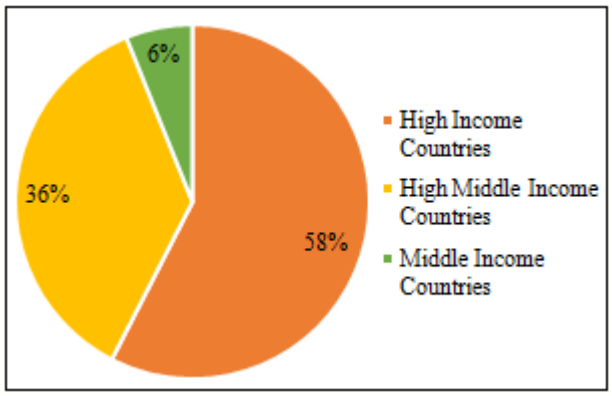

Figure 4: Geographical distribution of the included studies

Interventions

In accordance with the stage of cancer, the included studies were divided into two sub - groups: 1) early breast cancer (EBC) and 2) metastatic /advanced breast cancer (MBC/ABC).

Stages of breast cancer	Various drugs used
Early breast cancer	Taxanes (Paclitaxel or Docetaxel), Capecitabine, Nab - Paclitaxel, Sb - Paclitaxel, Doxorubicin, Cyclophosphamide, Epirubicin, Fluorouracil, Folinic Acid, Methotrexate, Mitomycin - C, Mitoxantrone, Thiotepa, Vincristine, Vindesine, Cisplatin, Carboplatin
Metastatic breast cancer	Cisplatin, Carboplatin, Paclitaxel, Docetaxel, 5 - Fluorouracil, Doxorubicin, Cyclophosphamide, Calusterone (androgenic steroid), Methotrexate, Chlorambucil, Ftorafur, Dibromodulcitol, Melphalan, Vinblastine, Mitoxantrone, Cytosine Arabinoside, Lomustine, Iphosphamide, Gemcitabine, Mitomycin, Vinorelbine, VP 16 (Etoposide), Mitolactol, Vindesine, Capecitabine, Tegafur (Pro - Drug Of Fluorouracil), Ixabepilone, Leucovorin, Antineoplaston A10, Adriamycin, Epirubicin, EribulinMesylate, Vincristine,

Taxanes (paclitaxel and docetaxel), platinum agents (cisplatin, carboplatin), anthracyclins (doxorubicin, epirubicin), cyclophosphamide, vincristine, vindesine and fluorouracil were found to be used equally for the treatment of both, early and advanced stages. The usage of Nab - paclitaxel, sb - paclitaxel, and thiotepa (an alkylating agent) was primarily used in early breast cancer treatment while chlorambucil, ftorafur, dibromodulcitol, melphalan, vinblastine, cytosine arabinoside, lomustine, iphosphamide, gemcitabine, vinorelbine, VP 16 (etoposide), mitolactol, tegafur, leucovorin, antineoplastonA10, adriamycin, eribulinmesylate and ixabepilone was identified across various studies which focused on the treatment of advanced/metastatic breast cancer.

Outcomes of the included studies

There were various outcomes estimated in the included reviews wherein24 (72.7%) studies had Overall Survival (OS) as their primary or secondary outcome measure while Disease Free Survival (DFS) was used as an endpoint in 11 (33.3%) studies. In the other 8 (24.2%) studies, Progression Free Survival (PFS) was evaluated while Quality of Life (QoL) and adverse events/ toxicity had been studied in 4 (12.1%) and 12 (36.4%) reviews respectively. Also, outcome measures like long term survival, long recurrence rate and mortality index was taken once in 3 different studies.

Quality of identified studies

To assess the quality of studies included in the review, PRISMA checklist was used to estimate scores for meta - analysis and systematic reviews whereas CONSORT checklist was used to estimate scores for Randomized controlled trial studies. As per the checklists used, "Yes" indicates a value of 1 that implies "correctly/sufficiently described", "Ns" indicates a value of 0.5 implying to "not sufficiently described" and "No" indicates value of 0 implying "incorrect or no information" regarding the specific topic in the study. While most of the studies lacked details on risk assessment, synthesis methods, biases, registration and protocol, none of them presented either methods employed or assessments of certainty (or confidence) in the body of evidence for each outcome that they assessed in their studies. The compiled scores ranged from 9.5 to 29.5, details of which are mentioned in the tables below.

Furthermore, Cohen's kappa statistic was calculated as a measure of quality assessment between the reviewers that demonstrated moderate agreement (κ = 0.549, % of agreement: 95.71%).

Consolidated PRISMA scores results

Authors	Year	Yes	Ns	No	Total scores
Asselain *et al.*	2018	19	9	4	23.5
Early Breast Cancer Trialists' Collaborative Group (EBCTCG)	2012	20	7	5	23.5
Van der Hageet *al.*	2007	22	5	5	24.5
Butters *et al.*	2010	25	4	3	27
Ding *et al.*	2018	17	8	7	21
Carrick *et al.*	2009	23	6	3	26
Belfiglio*et al.*	2012	13	11	8	18.5
Dear *et al.*	2013	24	4	4	26
Fujii*et al.*	2015	19	7	6	22.5
Lu *et al.*	2021	15	11	6	20.5
Egger *et al.*	2015	28	1	3	28.5
Xingfa*et al.*	2020	20	1	11	20.5
Egger *et al.*	2020	27	3	2	28.5

Ghersi*et al.*	2015	29	1	2	29.5
Li - Yang *et al.*	2015	20	5	7	22.5
Emilio *et al.*	2006	21	1	10	21.5
Miao *et al.*	2021	27	1	4	27.5
Qi *et al.*	2021	24	4	4	26
Weijiao*et al*	2015	18	6	8	21
Hackshaw*et al.*	2005	16	3	13	17.5
Qin *et al.*	2011	22	2	8	23
A'Hern*et al.*	1993	4	11	17	9.5
Xiao - Hua *et al.*	2016	22	5	5	24.5
Ze - Chun *et al.*	2016	23	9	0	27.5
Mazouni*et al.*	2007	12	6	14	15
Zheng *et al.*	2015	22	7	3	25.5
Shao *et al.*	2012	18	2	12	19
Lu *et al.*	2021	25	1	6	25.5
Ghanbari*et al.*	2015	17	7	8	20.5
Zaree*t al.*	2013	20	4	8	22
Jiang *et al.*	2012	20	5	7	22.5

Consolidated CONSORT scores results

Authors	Year	Yes	Ns	No	Total scores
Earl *et al.*	2012	32	4	8	34
Sparano *et al.*	2015	23	5	16	25.5

5. Key findings

Our analysis of early breast cancer treatments yields insights on strengths and pitfalls of various treatment regimens. Preoperative/neo - adjuvant (NACT) chemotherapy in EBC yields equivalent therapeutic outcomes (overall and disease - free survival) compared to postoperative/adjuvant chemotherapy (ACT) and still bestows additional benefits of increased breast conservation rates and reduced toxicity. However, it involves elevated risk of loco - regional recurrences compared to ACT which can although, be limited substantially if surgery remains part of the treatment even after complete tumour regression (16) . These findings are flanked by a EBCTCG study which reports similar conclusions on local recurrences if NACT was used to downscale the tumours. Though a study from China showed that the incorporation of anti - metabolite drugs (capecitabine) into a standard NACT regimen in EBC showed no improvement in DFS in all patients except for some subtypes with high risk of recurrence, and demonstrated a significantly high OS (17) . It also highlights insignificant difference in NACT and adjuvant therapy for distant recurrences, breast cancer mortality or death from any cause (18) . Besides, in a different review by Miao Liu *et al*, nab - paclitaxel was found effective for the treatment of non - metastatic breast cancer in the neoadjuvant setting (19) .

Numerous studies have also delved deep into adjuvant therapies to identify most effective combinations and sequences of chemotherapeutic drugs for optimal clinical benefits. Sensitivity analysis in a study by Ding *et al* demonstrates improved DFS and OS owing to TC (taxanes and cyclophosphamide) regimen and suggests their possibility of being non - inferior to anthracycline containing regimens which are otherwise associated with long term cardiotoxicities (20) . Fujii*et al* implement network meta - analysis for indirect comparison of regimens listed in the NCCN guidelines and platinum containing regimens. Toxicity associated with platinum containing regimens and comparatively poorer outcomes (OS) among patients treated with CMF or AC make sequential AC - T (sequential anthracycline - cyclophosphamide and taxane) likely to be the most effective adjuvant therapy regimen for EBC irrespective of hormone receptor status (21) . Similarly, a study found that sequential administration regimens as ACT provided a significant 12% reduction in mortality over the concurrent administration regimen in patients with node - positive EBC (22) . A 7 - year long follow - up study by Earl *et al* establishes E - CMF (epirubicin, cyclophosphamide, methotrexate and 5 - fluorouracil) as significantly superior to standard CMF (cyclophosphamide, methotrexate and 5 - fluorouracil) for all EBC patients (23) . Meta - analysis by Peto *et al* also attempts to compare different adjuvant polychemotherapy regimens and substantiates equivalence of standard CMF and standard 4AC (4 cycles of doxorubicin and cyclophosphamide) in reducing recurrence and breast cancer mortality (24) . Another long - term follow up study, aiming to establish the role and schedule of taxanes in operable EBC underscores the supremacy of sequential doxorubicin plus cyclophosphamide followed by weekly paclitaxel as an adjuvant chemotherapy option for Triple Negative Breast Cancer (TNBC) patients (25) .

Two studies illustrate the advantage of taxane - containing ACT regimens and note a significant benefit in both DFS and OS over standard chemotherapy in EBC (26) (27) . Its significance in diminution of risk of recurrence and death in early or operable breast cancer patients was reported by Ying - Yi Qin *et al* (28) . In another review centred around patients with operable breast cancer in early or advanced stages, C. Mazouni *et al* concludes a statistically significant improvement in pCR (pathological complete response) rate as a consequence of adding taxanes to anthracycline regimens (29) .

Similar to EBC, management of MBC has been the focal point for a multitude of researchers wherein they also compare survival advantage of combination chemotherapy over single - agent chemotherapy regimens. A study exploring the safety and efficacy of nab - paclitaxel mono - chemotherapy in MBC treatment (Lu *et al*), recognizes its benefit overweighing the associated harm which was assessed as generally manageable (30) .

Alternatively, combination chemotherapies although, were found to be significantly favorable in improving survival, tumor response and time to progression in MBC but were also linked to soaring toxicity (31, 32) . In contrast to this, the results of a study from the USA showed that the use of a combined taxane along with anthracycline regimen rather than a taxane - based regimen did not significantly improve OS in MBC patients (33) . Another review by Dear *et al* although, validates the above findings on higher response rate and toxicity associated with combination chemotherapy, does not observe any significant difference in overall survival between the two treatment strategies. It rather underpins the recommendations by international guidelines that suggest usage of sequential monotherapy in the absence of rapid disease progression (34) . Considerable advantage for TTP (time to progression) but not OS and ORR (overall response rate) were observed in MBC patients on

combination docetaxel vs those on single agent docetaxel, as per a meta - analysis review of phase III trials (35) . Also, for patients with MBC who received first - line combination chemotherapy with anthracycline, 5 - fluorouracil, adriamycin and cyclophosphamide, it was found that there was reduction in the proportion of patients with complete or partial tumour responses (36). In a study from U. K conducted in the 1993, increase in the odds of response, reduction in the hazard of dying by 22% and reduction of hazardof treatment failure by 31% was observed on inclusion of doxorubicin in Copper type regimen (42) .

Utilization of different chemotherapy regimens in metastatic TNBC patients has also been investigated by field experts. Capecitabine when combined with anthracycline/taxane regimens was found effective as first - line therapy to improve ORR and PFS (37) , while in early stage TNBC patients, this combination improved the OS, DFS in a study done in China byXingfaHuo*et al* (38) , two set of studies from China and Australia found that a carboplatin - based preoperative chemotherapy was acknowledged to produce significantly improved tumour response, pCR and BCS rates in comparison to non - carboplatin, in this subgroup (39) , (40) . Additionally, first line platinum - based chemotherapy was although associated with significantly benefits in ORRs and PFS in mTNBC patients, no significant difference was observed in OS (41) .

6. Discussion

Our review highlights the overlapping use of chemotherapeutic drug throughout the treatment pathway. Beyond standard compendia recommendations, clinician's discretion has been known as a decisive factor in utilization of such drugs on case - by - case basis. Incessant clinical research exploring optimal benefits of cytotoxic drugs and off - label prescriptions, being a common practice in oncology, makes it increasingly challenging and clinically inappropriate to group a drug to a specific stage.

This is the first review to the best of our knowledge that consolidates all the chemotherapeutic drugs used to treat breast cancer across its various stages. However, this study has its own limitations wherein we do not take into account the outcome measures of these drugs nor do we furnish comparative details on their efficacy and adverse effects. Furthermore, the comprehensive nature of the study is compromised owing to its exclusion of breast cancer occurring in men, reviews published in languages other than English, evidence from randomized controlled trials, observational studies and case reports.

Although this study sincerely strives to categorize utilization of various drugs based on the tumour progression, there is ample room for future research oriented to detailed estimation of their effect sizes on various clinically relevant end - points and health related quality of life, preferably through a meta - analysis. Such a study demonstrating incremental benefits of one over the other is extremely desirable to enrich the existing knowledge repository on breast cancer.

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