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Drug-Drug Interactions in Patients with Breast Cancer

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Abstract

The research paper investigates the intricate landscape of drug-drug interactions (DDIs) within the context of breast cancer treatment, with a particular focus on the elderly population and the use of complementary and alternative medicine (CAM). The study underscores the heightened susceptibility of elderly patients to DDIs due to the prevalence of polypharmacy and the widespread utilization of CAM among breast cancer patients. The potential ramifications of DDIs, encompassing adverse drug events and diminished treatment efficacy, are elucidated. The paper accentuates the imperative for healthcare providers to comprehensively understand both conventional and CAM therapies, enabling them to provide patients with informed guidance regarding safe and efficacious treatment options, culminating in enhanced patient outcomes.

Keywords

Breast Cancer, Drug-Drug Interactions, Polypharmacy, Side Effects, Anti-Cancer Drug Failure, Complementary and Alternative Medicine

1. Introduction

Breast cancer is the second leading cause of cancer-related death in women worldwide. Due to the prevalence of polypharmacy, which is the use of more medications than clinically necessary and at least one unnecessary drug, elderly cancer patients with comorbidities are more likely to experience adverse drug events, drug-drug interactions, increased mortality, and hospitalizations [1]. A group of enzymes, known as cytochrome P450s (CYPs), serves as catalysts for the oxidation of many endogenous compounds and xenobiotics [2]. CYPs, the main enzymes in drug metabolism and bioactivation, mediate about 75% of all drug metabolic processes. CYPs 1, 2, and 3 family members are the primary contributors to the oxidative

metabolism of more than 90% of therapeutic drugs among the 57 functional human CYP genes and 58 pseudogenes [3].

Traditional, time-limited cytotoxic chemotherapy regimens are replaced with continuous oral therapy with targeted drugs as part of an anti-cancer approach. Patients who may have comorbidities are prescribed targeted treatments for extended periods. Drug interactions can occur at all dosage levels, and either overdose or undertreatment can have serious clinical outcomes [4]. The median time to oral chemotherapy receipt from the day the order was written was eight days [4]. The provider performed toxicity checks at 30, 60, and 90 days for 80%, 65%, and 48% of the patients [5]. Potential drug interactions were observed in 55% of the patients [5]—drug-drug interactions through the use of experimental systems in drug development. Recent advances *in silico* approaches, such as pharmacokinetics modeling methods based on cheminformatics and physiological evidence, have been used to assess DDI potential but face challenges concerning reliability and accuracy [6].

With prevalence rates ranging from 23% in the United States to 63.2% in Türkiye among women over 65 years of age, polypharmacy increases with age and varies by nation [1]. Strategies must be developed to minimize unnecessary drugs in older women with cancer to improve their clinical outcomes [7]. Cancer patients use complementary and alternative medicine (CAM) to enhance survival rates, reduce side effects from therapy and cancer symptoms, and improve immune function [5]. Drug interactions are a major concern in cancer treatment, and they may impact plasma drug monitoring, which is crucial to optimizing antitumor action and reducing drug toxicity to normal tissue [8]. Several instances of these interactions between cytotoxic drugs have been discussed in the literature, including those involving methotrexate and NSAIDs and irinotecan and St. John's wort [4].

2. Breast Cancer Classification and Treatment

2.1. Hormone Receptor Status

Breast cancers can be classified as hormone receptor-positive, HER2-positive, or triple-negative, based on the presence or absence of specific proteins (estrogen receptors, progesterone receptors, human epidermal growth factor receptor 2, or HER2) in cancer cells.

- **Hormone Receptor-Positive.** These cancers are treated with hormone therapy, which can block the effects of estrogen on cancer cells. Options include tamoxifen, aromatase inhibitors, and ovarian suppression therapy.
- **HER2-Positive.** These cancers are treated with targeted therapy drugs targeting the HER2 protein, such as trastuzumab (Herceptin), pertuzumab (Perjeta), and ado-trastuzumab emtansine (Kadcyla), in combination with chemotherapy.
- **Triple-Negative.** These cancers do not have estrogen receptors, progesterone receptors, or excess HER2 protein. They are more challenging to treat and often

require chemotherapy. Some triple-negative cancers may be treated with immunotherapy if they have a high protein level called PD-L1.

2.2. Stages of Cancer

The stage of the cancer (how much the cancer has spread) is a key factor in determining treatment. Early-stage cancers can be treated with surgery and possibly radiation therapy, while more advanced cancers may also require chemotherapy, hormone therapy, or targeted therapy. The stage of breast cancer can affect the available treatment options and the outlook for the cancer. It is essential to discuss the stage of breast cancer with the healthcare team and to work together to develop a treatment plan that is tailored to the patient's specific circumstances.

- **Stage 0 (Carcinoma *in situ*).** This is the earliest stage of breast cancer, in which the cancer is confined to the ducts or lobules of the breast and does not spread to surrounding tissue. Stage 0 breast cancer is typically treated with surgery, and in some cases, radiation therapy may also be recommended.
- **Stage I.** At this stage, the cancer is still relatively small and has not spread to the lymph nodes. Stage I breast cancer is usually treated with surgery, and radiation therapy may also be recommended, especially if the cancer is hormone receptor-positive.
- **Stage II.** At this stage, the cancer is more prominent and may have spread to the lymph nodes. Stage II breast cancer is generally treated with a combination of surgery, radiation therapy, and possibly chemotherapy, hormone therapy, or targeted therapy.
- **Stage III.** At this stage, the cancer is more significant and has spread to the lymph nodes and possibly to other tissues near the breast. Stage III breast cancer is generally treated with a combination of surgery, radiation therapy, chemotherapy, hormone therapy, and/or targeted therapy.
- **Stage IV (Metastatic).** At this stage, the cancer has spread to other parts of the body, such as the bones, lungs, or liver. Stage IV breast cancer is generally treated with a combination of chemotherapy, hormone therapy, and/or targeted therapy. Although this stage is not curable, it is often treatable, and many people with Stage IV breast cancer can live for many years with the disease.

2.3. Grade of Cancer

The cancer grade provides valuable insights into its biological aggressiveness and potential clinical behavior. It is determined through microscopic examination of cancer cells, assessing their degree of abnormality and their estimated rate of growth and spread. This assessment is frequently conducted using standardized systems such as the Nottingham grading system, which assigns a numerical grade based on specific histological criteria. High-grade cancers, characterized by marked cellular atypia and rapid proliferation, necessitate more aggressive therapeutic interventions to achieve effective disease control. Conversely, lower-grade cancers,

exhibiting less cellular disarray and slower growth patterns, may be amenable to less intensive treatment modalities. The tumor grade also carries prognostic significance, with higher grades generally associated with a less favorable clinical outcome.

2.4. Age and Overall Health

A patient's age and overall health status are critical determinants in the formulation of breast cancer treatment plans. Older adults and individuals with comorbidities may exhibit diminished tolerance to certain therapies due to age-related physiological changes or the presence of concomitant medical conditions. For instance, the incidence and severity of chemotherapy-induced side effects may be heightened in older patients due to decreased organ function, while certain targeted therapies may be contraindicated in patients with pre-existing cardiovascular disease. Consequently, treatment plans must be individualized to accommodate these patient-specific factors, potentially necessitating dose adjustments, alternative therapeutic regimens, or intensified monitoring for adverse events. In the context of older adults, a comprehensive geriatric assessment is instrumental in evaluating their functional status, comorbidities, and social support network, facilitating the selection of the most appropriate and tolerable treatment approach.

2.5. Genetic Factors

Inherited genetic mutations can profoundly influence an individual's susceptibility to breast cancer and the selection of optimal treatment strategies. Mutations in the BRCA1 and BRCA2 genes, in particular, confer a substantially elevated lifetime risk of developing breast and ovarian cancer. Individuals harboring these mutations may elect to pursue proactive risk-reducing measures, such as intensified surveillance, prophylactic surgery (mastectomy or oophorectomy), or chemoprevention. However, the landscape of breast cancer susceptibility genes extends beyond BRCA1/2, encompassing mutations in other genes like PALB2, ATM, and CHEK2, which can also impact treatment decisions. Genetic testing and counseling are indispensable in identifying these mutations and guiding personalized treatment plans.

2.6. Personal Preference

The paradigm of shared decision-making is integral to contemporary cancer care. Patients' preferences and values warrant careful consideration alongside clinical evidence when determining the most suitable treatment course. Factors such as desired quality of life, concerns regarding treatment-related adverse effects, and individual beliefs about different therapeutic modalities can all influence a patient's treatment preferences. Some individuals may prioritize aggressive treatment options to maximize the likelihood of a cure, even if it entails enduring more significant side effects. Others may opt for less invasive approaches with potentially

fewer adverse effects, even if it carries a slightly higher risk of disease recurrence. Providing comprehensive patient education, encompassing clear and unbiased information about the benefits and risks of each treatment option is paramount in empowering patients to make informed decisions congruent with their individual goals and values.

2.7. Treatment

The best treatment for breast cancer will depend on the specific characteristics of the cancer, including the type of breast cancer, the stage of the cancer, and general health and preferences. There is no one-size-fits-all approach to the treatment of breast cancer, and a variety of treatment options may be considered. Some standard treatment options for breast cancer include:

- **Surgery.** Surgery may involve lumpectomy (removal of the tumor and some surrounding tissue) or mastectomy (removal of the entire breast).
- **Radiation Therapy.** Radiation therapy uses high-energy radiation to kill cancer cells or prevent them from growing. It may be used after surgery to reduce the risk of cancer coming back.
- **Chemotherapy.** Chemotherapy uses drugs to kill cancer cells or prevent them from growing. It may be used before surgery to shrink the tumor, after surgery to reduce the risk of cancer coming back, or, in the case of metastatic breast cancer, to slow the spread of the cancer.
- **Hormone Therapy.** Hormone therapy may be used to treat hormone receptor-positive breast cancer. It works by blocking the effects of estrogen on cancer cells.
- **Targeted Therapy.** Targeted therapy uses drugs or other substances to identify and attack specific cancer cells without harming normal cells. It may be used to treat HER2-positive breast cancer.
- **Immunotherapy.** Immunotherapy may be used to treat triple-negative breast cancer that has a high level of a protein called PD-L1. It works by helping the immune system fight cancer. The best treatment plan will be tailored to the individual's specific circumstances and will consider the person's preferences and values. A multidisciplinary team of healthcare professionals, including surgeons, oncologists, radiologists, and pathologists, will work together to develop a treatment plan most likely effective for the individual. It is important for people with breast cancer to be involved in the decision-making process and to feel comfortable with the treatment plan that is chosen.

2.8. Pain and Treatment

Pain associated with cancer treatment can vary widely from person to person and can depend on the specific treatment received, the individual's tolerance to pain, and the presence of other health conditions. However, some treatments are generally considered less painful than others. For example, hormone therapy and targeted therapy are often well tolerated and may cause only mild side effects, such

as hot flashes, fatigue, and nausea. These treatments are typically administered orally or intravenously and do not cause pain during administration. Chemotherapy can cause more significant side effects, including pain, but pain is usually manageable with pain medications. Some people may also experience pain at the site of injection or infusion. Surgery and radiation therapy can cause more immediate pain, especially during and immediately after treatment. However, both treatments are typically followed by a period of recovery, during which pain should decrease. It is important to note that the pain associated with cancer treatment is often temporary and can be managed with medications and other pain management strategies. A healthcare team will work with the patient to develop a plan to manage pain and other side effects. It is also worth noting that the effectiveness of a treatment can also be a factor in the associated pain. Although some treatments may be less painful, they may not be as effective in treating the cancer. Ultimately, the decision on which treatment to receive will depend on the individual's specific circumstances and the advice of his healthcare team.

3. Kinase Inhibitors and Their Role in Breast Cancer Treatment

An important class of anti-cancer medications is kinase inhibitors (KIs). Many are human cytochrome P450 (CYP) substrates and inhibitors, increasing the risk of undesirable drug interactions [3]. Eleven kinase inhibitors are approved by the U.S. Food and Drug Administration [9]. In a study, the impact of a library of K-I, which included 11 KIs that have received FDA approval, was tested on human CYP1A2, CYP2D6, 2C9, and 3A4. Inhibition of CYP1A2, 2D6, 2C9, and 3A4 was significantly inhibited by 80 compounds, or around 13% [1]. These findings imply that many KIs can operate as CYP inhibitors, and more research is required to determine how they can affect patients' health [1]. Computational methods like molecular coupling offer insights into drug-enzyme interactions, aiding in drug design and toxicity prediction, but improvements in virtual screening are necessary for more accurate metabolism site prediction [10].

Cyclin-dependent kinase 4/6 inhibitors (CDK4/6 inhibitors) have demonstrated remarkable efficacy in treating advanced breast cancer, particularly when combined with endocrine therapy. However, their metabolism involves CYP3A and SULT2A1 enzymes, necessitating careful consideration of potential DDIs with other medications metabolized by these enzymes. The three approved CDK4/6 inhibitors exhibit varying adverse effect profiles, with abemaciclib associated with higher rates of diarrhea and fatigue, while palbociclib is linked to neutropenia and gastrointestinal toxicity. Effective management of these side effects through dose adjustments and close monitoring is crucial for successful treatment outcomes [11]-[13].

The enzymes CYP3A and SULT2A1 are involved in the metabolism of the three CDK4/6 inhibitors, and CYPA3A mediates the liver metabolism of ribociclib. One of the three inhibitors should not be used with a strong (such as phenytoin or

clarithromycin) or moderate (such as modafinil, abemaciclib, or modafinol) CYP-3A inhibitor. The use of CYP 3A inhibitors may increase, which may result in increased toxicity or reduced efficacy for some medications [13]. Compared to the other two CDK4/6 inhibitors, abemaciclib exhibits a higher rate of diarrhea and tiredness but a lower rate of hematologic side effects, such as neutropenia and nausea. Neutropenia, leukoencepenia, fatigue, and nausea are the most frequent adverse effects of Palbociclib. The most frequent grade 3/4 side events in the MONARCH-1 study were hypertension, elevated levels of ALT/AST, and lymphopenia [14].

Neutropenia and gastroinotoxicity are the main adverse effects of CDK4/6-inhibitor-based combination therapy, such as Palbociclib. However, there are some variances for other drugs. In contrast to chemotherapy, toxicity can be controlled by changing the dose. Successful treatment depends on early and adequate monitoring, regular clinical evaluations, and control of adverse effects [13].

In a study involving patients receiving palbociclib in conjunction with endocrine therapy, 38 patients (38.0%) required dosage adjustments. The majority of these adjustments (81.6%) were implemented during the second and third treatment cycles. The most prevalent treatment-related adverse events necessitating dosage modification were neutropenia (grades 3 - 4, 54.8%) and mucositis (grades 1 - 3, 9.5%). The most frequent dosage modification among these 38 patients was a reduction from the standard 125 mg daily dose of palbociclib to 100 mg daily (65.8%). Less frequent adjustments included delaying or restarting the full dose or modifying the administration schedule (7.9%) [15].

One of the most reported adverse effects of TKI therapy with a TKI is diarrhea, a typical side effect of many cancer therapies. Depending on the drug, the reported incidence of all-grade diarrhea for various TKI in Breast cancer ranges from 18 to 95% [16].

The mainstay of the pharmacological therapy for uncomplicated mild to moderate diarrhea is loperamide, which is recommended in the prescription of advice both as prevention and after the beginning of diarrhea [17]. When diarrhea does not disappear despite the use of antidiarrheal medications, therapy should be postponed until grade 1 diarrhea has occurred [18]. Patient education is essential to help patients recognize the symptoms and indications of diarrhea and emphasize the urgency of immediate treatment [19].

4. Cam Compounds and Their Interactions with Conventional Therapies

The widespread use of complementary and alternative medicine (CAM) among cancer patients underscores the need for healthcare providers to be knowledgeable about these therapies and their potential interactions with conventional treatments [20]. Cancer patients can reduce the various side effects because of chemotherapy due to the link between natural products and ACD [5]. Due to the interaction between the drug and the natural substance, this relationship involves risks

that outweigh the actual benefits [5]. While CAM can offer benefits in managing side effects, the risk of drug-herb interactions, particularly those affecting CYP enzymes involved in drug metabolism, cannot be overlooked. These interactions can alter drug pharmacokinetics and pharmacodynamics, leading to therapeutic ineffectiveness or toxicity [5].

The amount of medication that reaches the target site may change due to metabolic interactions, leading to therapeutic ineffectiveness or even toxicity from overdose [21]. The supply of phytochemicals and the cytochrome system together is not recommended and can be detrimental. One of the most frequent alterations in these interactions is the potential activation or inhibition of CYPs that metabolize ACDs [21]. Prebiotics, probiotics, fungi, and plants should no longer be considered separate dietary supplements but possible adjuvants in traditional pharmacological therapy. Red ginseng and ginger help reduce the most typical gastrointestinal adverse effects of ACD use, nausea, and vomiting (6-gingerol) [5].

A study finds that CAM therapies can be cost-effective for various conditions, and it emphasizes the importance of economic evaluations to guide evidence-based clinical practice and health policies. Furthermore, the paper points out the need for better quality data on CAM therapies, which the lack of participation of practitioners in research can hinder [22].

4.1. Herbal Supplements and CAM Compounds

- **St. John's Wort.** A popular herbal remedy for depression, it significantly induces CYP3A4 and other CYP enzymes. This can reduce the effectiveness of many chemotherapy drugs, including tamoxifen, irinotecan, and some kinase inhibitors.
- **Ginseng.** Research suggests that it can affect CYP enzymes and alter the metabolism of certain drugs. Potential interactions exist with medications used for blood clotting and diabetes management.
- **Ginger.** Ginger is commonly used for nausea but can interfere with blood-thinning medications.
- **Garlic.** It can increase the risk of bleeding, especially when combined with blood thinners or non-steroidal anti-inflammatory drugs).
- **Red Ginseng.** This may reduce the effectiveness of chemotherapy agents metabolized by CYP3A4, potentially affecting treatment outcomes.
- **Phytoestrogens (Soy, Red Clover).** These naturally occurring compounds can mimic estrogen. Potential interactions with hormone-based therapies, such as tamoxifen, raise concerns about reduced effectiveness or increased estrogenic side effects.

4.2. Vitamins and Minerals

- **Vitamin E.** High doses may interfere with the effectiveness of tamoxifen.
- **Calcium.** Some studies suggest high calcium intake during chemotherapy might negatively impact the results.

- **Antioxidants.** The concern is that particular antioxidants could protect cancer cells from the effects of chemotherapy or radiation therapy.

4.3. Food-Herb-Drug Interactions

- **Grapefruit Juice.** Contains compounds that inhibit CYP3A4, potentially leading to increased blood levels and toxicity of numerous medications, including specific chemotherapy agents and kinase inhibitors.

4.4. Specific Examples of CAM-Conventional Drug Interactions

- **St. John's Wort & Chemotherapy.** The induction of CYP3A4 by St. John's Wort can significantly reduce the blood levels and effectiveness of several chemotherapy drugs, such as irinotecan and docetaxel.
- **Ginseng & Warfarin.** Ginseng's impact on CYP enzymes can alter warfarin metabolism, potentially leading to increased bleeding risk due to elevated warfarin levels.
- **Ginger & Antiplatelet Drugs.** The combination of ginger and antiplatelet medications like aspirin or clopidogrel can heighten the risk of bleeding due to their synergistic effects on platelet function.
- **Garlic & Antiretroviral Drugs.** Garlic can decrease the effectiveness of certain antiretroviral medications used in HIV treatment by inducing CYP3A4, leading to subtherapeutic drug levels.
- **Soy Isoflavones & Tamoxifen.** The estrogenic activity of soy isoflavones may interfere with tamoxifen's action in hormone receptor-positive breast cancer, potentially reducing its effectiveness.

4.5. Challenges and Considerations in Managing CAM-Related DDIs

- **Lack of Comprehensive Data.** The limited scientific evidence on the full spectrum of potential interactions between CAM and conventional cancer drugs poses a significant challenge in risk assessment and patient counseling.
- **Patient Underreporting.** The reluctance of patients to disclose their CAM use to healthcare providers can hinder the identification and management of potential DDIs, leading to adverse events and compromised treatment outcomes.
- **Variability in CAM Products.** The lack of standardization and quality control in CAM products makes it difficult to accurately assess their composition, potency, and potential interactions with conventional medications.
- **Limited Healthcare Provider Knowledge.** The knowledge gap among healthcare providers regarding CAM therapies and their potential interactions can impede effective communication and guidance to patients, potentially increasing the risk of DDIs.
- **Complex Patient Profiles.** The presence of comorbidities and polypharmacy in breast cancer patients, especially in older populations, further complicates the management of DDIs, requiring a personalized and vigilant approach to medication reconciliation and monitoring.

5. Polypharmacy and Its Implications for Elderly Cancer Patients

Polypharmacy is a prevalent concern among elderly cancer patients, often exacerbated by comorbidities. This increases the risk of DDIs and adverse drug events (ADEs) due to competition within the CYP enzyme system, altered drug metabolism due to comorbidities, and increased sensitivity to side effects in older patients. Complex medication regimens can also lead to confusion and errors. Proactive medication management, patient education, and minimizing unnecessary drugs are crucial in mitigating these risks and improving treatment outcomes for this vulnerable population [23].

In a study between the older and non-elderly groups, the prevalence of comorbidity and polypharmacy in breast cancer patients were identified and compared. The most frequently reported comorbid conditions were arthritis, hypertension, and diabetes. The comorbidity was comparable to population reports and previous breast cancer research. The prevalence of gastrointestinal disorders was relatively high in both groups. This study is the first to highlight the importance of polypharmacy in patients over 65 years of age. Control groups without cancer had a lower frequency of comorbidity than older people with cancer. According to this study, only two individuals had no comorbid conditions, while up to 99% of patients 65 and older had at least one. The senior group had significantly higher levels of comorbidity ($p = 0.001$). The study observed a higher prevalence of several chronic conditions in elderly individuals compared to their younger counterparts. These conditions included diabetes, hypertension, gastrointestinal disorders, heart disease, and hyperlipidemia.

Furthermore, aging adults were more likely to experience asthma, depression/anxiety disorders, respiratory diseases, and musculoskeletal conditions. These findings have been frequently demonstrated in the historical process and are compatible with the literature. Research reveals that the elderly population used more medications on average, including PPI, ACEI-ARB, diuretics, beta-blockers, calcium channel blockers, anti-aggregant/anticoagulant, oral anti-diabetics, insulins, NSAID, inhaler treatment, vitamin D or/and calcium, bisphosphonates, and other pharmaceuticals. The incidence of drug usage was as expected when comorbid disorders were considered [1].

In another study, polypharmacy is brought on by the rise of elderly patients and/or people with both cancer and other chronic diseases [4]. Since cytochrome P450 enzymes are primarily responsible for the metabolism of TKI and mTOR inhibitors, the danger of drug-drug interactions (DDIs) becomes a clinically significant concern. Depending on these DDI, exposure to anti-cancer drugs may vary [4]. Polypharmacy (multiple medications) is common in elderly cancer patients, who often have comorbidities. This increases the risk of DDI and ADEs due to:

- Drugs compete within the CYP enzyme system, leading to unpredictable drug levels.

- Comorbidities alter drug metabolism, potentially causing toxicity.
- Elderly patients are more sensitive to side effects.
- Complex medication regimens increase confusion and errors.

These factors can lead to severe ADE, hospitalizations, compromised treatment, and worsening quality of life. Proactive medication management, patient education, and minimizing unnecessary drugs are crucial.

6. Drug Classes and Their Associated Toxicities

Antimetabolites. In one of the first cancer drug families, antimetabolites only include tiny compounds as their constituents. The prototypical folic acid analog methotrexate can be made worse by the nephrotoxic drug cisplatin—the failure to synthesize DNA and RNA results in hepatotoxicity [24]. A prominent example of a pyrimidine analog with negative consequences is 5-fluorouracil (5-FU), which can cause bleeding, leukopenia, thrombocytopenia, and other GI problems. However, the method of administration and the duration of therapy affect these toxicities [24].

For women under 50 years of age and those between 50 and 69 years of age, chemotherapy lowers the yearly mortality rate from breast cancer by 38% and 20%, respectively. However, with four rounds of doxorubicin and cyclophosphamide treatment, there is a known risk of cardiotoxicity, with 17% of patients experiencing cardiac problems [25].

Peak exercise SV and CO, as well as skeletal oxygen utilization, are reduced in post-anthracycline-treated BC Survivor women compared to matched controls. According to a mediation study, more significant myocardial fibrosis was associated with poorer exercise capacity and lower peak VO2. An overlooked factor in women with and without breast cancer's cardiovascular risk is fatty infiltration of the thigh muscle [26].

The BILCAP study compared adjuvant capecitabine with observation in patients with biliary tract cancer who underwent surgery with curative intent. Although the primary endpoint of overall survival did not reach statistical significance, the sensitivity analyses showed benefits in overall survival and recurrence-free survival [27]. Deferred recurrence occurred in the capecitabine group, and long-term survival analyses will be reported once five years of follow-up have been met. Adjuvant capecitabine improved overall survival compared to observation following surgery for biliary tract cancer, with a median overall survival of 24 months in the capecitabine group and 17 months in the observation group, suggesting a 7-month increase in OS with capecitabine treatment. The limitations include its long recruitment period of 10 years and the evolving approaches to clinical trials during this period [27].

Alkylating Agents. A nitrogen mustard-type alkylating agent called cyclophosphamide is associated with myelosuppression, neutropenia, anemia, and thrombocytopenia. Small molecules such as DNase, p53, and MAP kinase are also included in this class of cancer drugs. Black-box warnings for nausea and vomiting

associated with cisplatin can be avoided using antiemetic medications [24].

The study found that low-dose CPA-induced hyponatremia was relatively common in breast cancer patients, but it usually resolved without any specific treatment [28]. Researchers identified age and pretreatment serum sodium levels prior to treatment as independent risk factors for hyponatremia. However, selection bias is possible since this was a single-center study with a small sample size. Therefore, more large-scale studies are needed to confirm these findings and assess the clinical significance of low-dose CPA-induced hyponatremia in breast cancer patients [28].

The loss of appetite results in a decrease in BMI, which is beneficial in one aspect, as a research paper found that a higher body-mass index (BMI) was significantly associated with increased mortality rates due to breast cancer in women. The study also estimated that current patterns of overweight and obesity in the United States could account for 20% of all deaths from cancer among women [29].

Antimitotic Agents. Breast cancer is one of many solid tumors that can be treated with docetaxel. Patients' metastatic, radiation and neoadjuvant results can be improved. Patients with hormone receptor-positive or hormone receptor-positive breast cancer at high risk of the disease returning may consider adjuvant chemotherapy. The Western Hemisphere has seen a significant decline in cause-specific mortality from breast cancer due to adjuvant systemic chemotherapy [29]. The findings suggest that paclitaxel plus bevacizumab combination therapy may be a viable option for women with primary breast cancer, as it significantly improved progression-free survival and objective response rates compared to paclitaxel alone [30].

Although overall survival rates between the two treatment modalities were similar, it is crucial to consider the potential risks associated with specific modern treatments, such as accelerated partial-breast irradiation and intensity-modulated radiation therapy, mainly when their use may only result in minor improvements in overall survival [30]. The study also highlights the clinical importance of targeting the VEGF receptor pathway and the potential utility of angiogenesis inhibitors, such as bevacizumab, in the treatment of primary breast cancer. These findings may have significant implications for the development of future therapies in this area [30].

One of the cytotoxic drugs that commonly induces acute infusion responses is docetaxel. Typical "standard" and "classical hypersensitivity" reactions are among them (*i.e.* angioedema, urticaria, wheezing, stridor, anaphylaxis, and cardiorespiratory). Before infusion, premedication with glucocorticoids and antihistamines helps reduce the severity of these responses [31].

Myelosuppression reduces white cell count (or neutrophil count) after chemotherapy treatment and can occur 10 - 14 days after initial administration. Patients who develop this condition are at increased risk of serious infections and often require hospitalization, resulting in a dose reduction of docetaxel. Docetaxel treatment commonly causes fluid retention that manifests itself as pericardial effusion,

pleural effusion, and extremity edema. One of the hypothesized causes for this unfavorable effect is enlarged capillaries, which cause fluid to leak into the tissue around them. Therapy with diuretics can minimize the severity of fluid retention and relieve symptoms [31]. Docetaxel, a chemotherapy drug, is associated with several adverse drug reactions (ADRs), including neutropenia, anemia, thrombocytopenia, peripheral neuropathy, and alopecia. Patients should report any new symptoms during treatment to ensure prompt treatment. Long-term effects result in tingling, numbness, and loss of sensation, categorized into sensory and motor neuropathy [29]. In docetaxel treatment, early detection of symptoms, followed by a delay in medication or dosage decrease, helps to reduce its ADRs (adverse drug reactions). The main clinical signs are numbness, tingling in the hands and feet, and reflex loss. Taxane-induced neuropathy may benefit from symptomatic relief with anticonvulsants such as gabapentin [31].

Hormonal Therapy. Hormonal therapy, although practical, faces adherence challenges, with approximately one-third of patients discontinuing treatment before the recommended 5-year duration. This premature cessation is primarily attributed to adverse symptoms associated with estrogen deprivation. Among these, myalgias and arthralgias are particularly prevalent, affecting up to 30% of women receiving aromatase inhibitors (AIs) therapy. Consequently, it is imperative that patients initiate AI treatment with a baseline assessment for osteopenia and osteoporosis, given the increased risk of bone loss associated with these medications [32].

According to studies, women who produce more estrogen have a higher chance of developing breast cancer. Stimulation of breast cell proliferation by the estrogen receptor (ER) and the conversion of estradiol to genotoxic metabolites have both been suggested as potential explanations for the increased risk. The research is based on the idea that genotoxic and receptor-mediated mechanisms contribute to breast cancer. The enzymes required to convert estradiol were first shown to exist in MCF-7 breast cancer cells and normal breast tissue in mice transfected with aromatase. The effects of castration-induced estrogen depletion and the role of the estrogen receptor (ER) alpha on tumor development were then studied in ER knockout/Wnt-1 (ERKO/Wnt) transgenic rats. Lastly, in noncastrate, ER KO/Wnt mice later evaluated the impact of an aromatase inhibitor on tumor incidence [33].

Studies have shown that the risk of breast cancer recurrence is significantly reduced in patients who suffer vasomotor symptoms within the first three months of therapy. The dependence on the reported toxicity of physicians is a significant obstacle and may have led to underestimating the burden [34]. Data on the genetic factors that influence the AI response are few, especially in the front-line metastatic situation. Although the polymorphisms CYP19A1 and CYP1A2 are alluring response indicators, little data supports their therapeutic value. To clarify the function of these genes, more research is needed in prospectively recruited breast cancer patients [32].

Aromatase inhibitors are only used in postmenopausal cases, while LHRH analogs may also be prescribed to premenopausal women. Around 50% of hormone-dependent cancers become resistant over time, but certain molecules such as Palbociclib and Everolimus have effectively reversed this resistance [35]. Tamoxifen (SERM) is a selective estrogen receptor modulator that increases the risk of posterior subcapsular cataracts. It also affects perception similarly to aromatase inhibitor (AI) but in an age-dependent manner, suggesting that a change towards lower levels of estrogen activity is more critical than low estrogen activity itself [36].

Immunotherapy Agents. Combining pertuzumab with trastuzumab, which each inhibits a separate domain of the HER2 receptor, efficiently treats HER2-positive breast cancer [37]. According to clinical trials, pertuzumab is typically safe and beneficial for patients, although it can occasionally result in severe cardiac damage [25] [37]. The most common but often mild side effect is diarrhea. Some researchers suggested that pertuzumab may not significantly assist patients with small primary tumors. In general, the study emphasizes the need for careful patient selection and monitoring by highlighting the possible advantages and disadvantages of combination therapy targeting particular subtypes of breast cancer [37].

In the TRYPHAENA study, the anthracycline regimen was associated with more significant febrile neutropenia than the nonanthracycline regimen and secondary leukemia and cardiotoxicity. The percentage of patients receiving G-CSF support between the two therapy groups was relatively similar [25]. Although they still showed unfavorable toxicity levels, nonanthracycline chemotherapy regimens for breast cancer were shown to have a more favorable toxicity profile. Most of the patients in both groups had grade 2 or worse neuropathy, and treatment techniques are being researched. The typical and bothersome side, diarrhea, tends to increase when administered with a taxane-carboplatin [25].

A study analyzed 1,045 breast tumor samples to identify differential immune signatures associated with survival using gene expression profiling techniques. They established a TAIG (tumor-associated immune gene) risk model to predict poor survival outcomes for patients with advanced pathological stages or higher stages of AJCC-TNM based on high TAIG levels correlated with these clinical characteristics. Additionally, analysis of the TIMER database revealed adverse associations between TAIG levels and various types of infiltrating lymphocytes. This research provides valuable information on potential targets for immunotherapy treatment options and highlights the importance of understanding the interactions between different components within the tumor microenvironment [12].

Trastuzumab is a monoclonal antibody used to treat metastatic breast cancers that overexpress HER-2. HER-2 is a member of the EGFR family that regulates cell proliferation and survival. Trastuzumab is rarely associated with significant skin toxicity, unlike anti-EGFR targeted therapies, and this may be explained by the lack of detectable functional HER-2 heterodimers in human keratinocytes,

which is different from the EGFR dimerization.

7. Conclusions

Breast cancer treatment necessitates a multifaceted approach, particularly for elderly patients at risk of polypharmacy and DDIs. Understanding CYP enzymes' role in drug metabolism is crucial for both conventional and CAM therapies. While CAM offers potential benefits, healthcare providers and patients must be aware of potential interactions with conventional drugs. Research should focus on investigating CAM effectiveness and potential metabolic interactions.

Kinase inhibitors (KIs), a vital class of anti-cancer medications, often interact with CYP enzymes, highlighting the need for careful research to predict potential DDIs. In particular, cyclin-dependent kinase 4/6 inhibitors (CDK 4/6) have shown remarkable efficacy in breast cancer treatment. However, close monitoring of adverse effects, such as neutropenia and gastrointestinal problems, is essential to manage DDIs and dosage adjustments. Patients should be fully informed about possible side effects like diarrhea and informed about prompt symptom management.

The widespread use of CAM highlights its potential benefits, but healthcare providers must be knowledgeable about these modalities to ensure safe integration with conventional therapies. Research should prioritize investigating the effectiveness of CAM alongside the potential for metabolic interactions that could affect the efficacy of anti-cancer drugs.

Polypharmacy in elderly cancer patients underscores the need for rational drug use, robust clinical follow-up, and medication awareness programs. Addressing polypharmacy can significantly improve treatment outcomes.

In conclusion, successful breast cancer management requires a multifaceted approach. Healthcare providers must be informed about the complexities of drug interactions, including those involving CAM, to personalize treatment plans, optimize results, and minimize adverse events. More research is needed to understand the interaction between conventional and complementary therapies fully and to develop strategies that reduce the risks associated with polypharmacy, especially in older patients.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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List of Symbols

ACD	Anti-cancer drugs
ACEI-ARB	Angiotensin-converting enzyme inhibitors-angiotensin II receptor blockers
ADR	Adverse drug reactions
AI	Aromatase inhibitor
AIS	Aromatase inhibitors
AJCC-TNM	American Joint Committee on Cancer-tumor, node, metastasis
BC	Breast cancer
BMI	Body mass index
CAM	Complementary and alternative medicine
CDK 4/6	Cyclin-dependent kinase 4/6 inhibitors
CPA	Cyclophosphamide
CYPs	Cytochrome P450s
DDIs	Drug-drug interactions
EGFR	Epidermal growth factor receptor
ER	Estrogen receptor
ERKO/Wnt	Estrogen receptor knockout/Wnt-1
5-FU	5-fluorouracil
G-CSF	Granulocyte colony-stimulating factor
GI	Gastrointestinal
KIs	Kinase inhibitors
mTOR	Mammalian target of rapamycin
NSAID	Non-steroidal anti-inflammatory drugs
OS	Overall survival
PPIs	Proton pump inhibitors
SERM	Selective estrogen receptor modulator
TAIG	Tumor-associated immune gene
TKI	Tyrosine kinase inhibitors
VO2	Oxygen consumption