




Resistance and Overcoming Resistance in Breast Cancer

This article was published in the following Dove Press journal:
Breast Cancer: Targets and Therapy

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Abstract: The incidence and mortality of breast cancer (BC) have increased in recent years, and BC is the main cause of cancer-related death in women worldwide. One of the most significant clinical problems in the treatment of patients with BC is the development of therapeutic resistance. Therefore, elucidating the molecular mechanisms involved in drug resistance is critical. The therapeutic decision for the management of patients with BC is based not only on the assessment of prognostic factors but also on the evaluation of clinical and pathological parameters. Although this has been a successful approach, some patients relapse and/or eventually develop resistance to treatment. This review is focused on recent studies on the possible biological and molecular mechanisms involved in both response and resistance to treatment in BC. Additionally, emerging treatments that seek to overcome resistance and reduce side effects are also described. A greater understanding of the mechanisms of action of treatments used in BC might contribute not only to the enhancement of our understanding of the mechanisms involved in the development of resistance but also to the optimization of the existing treatment regimens.

Keywords: breast cancer, endocrine therapy, chemotherapy, resistance, emerging treatments

Introduction

Cancer is a common disease and represents one of the biggest health problems in the world and a significant global concern. The incidence and mortality rates of breast cancer (BC) have increased in recent years, and BC is currently the leading cause of cancer death in women worldwide.¹ Decision making for the treatment of patients with BC is primarily based on the assessment of clinical and pathological parameters. In particular, the immunohistochemical evaluation of prognostic factors, such as estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor 2 (HER2) are critical for tumor subtype classification and histological grade, which play an important role in determining therapeutic strategies. For example, patients with ER-positive (ER+) tumors receive endocrine therapy, and a small fraction of these patients also receive chemotherapy. Patients with HER2-positive tumors (HER2 enriched or HER2+) are treated with antibodies directed against HER2 or small-molecule inhibitors in combination with chemotherapy. Patients with triple-negative tumors receive mainly chemotherapy.²⁻⁴

BC is a heterogeneous and complex disease in which each patient has unique morphological and molecular features, rather than a disease in which only a few genes, proteins, and/or signaling pathways contribute to disease progression in a simple, independent, and autonomous manner. Studies have shown that patients with the same type

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of BC can show differential responses to treatment, which further indicates the high heterogeneity in this disease. Despite the great technological advances that have enhanced our understanding of human cancers as heterogeneous diseases, current clinicopathological and molecular parameters leave a significant number of patients at risk of over-treatment and side effects.

Currently, drug-resistant BC is treated by selecting other drugs, without understanding the molecular mechanisms involved in the resistance of a given case. Better understanding of the mechanisms involved in the development of resistance might not only reduce the adverse effects of treatment but also lead to the development of new strategies for improving diagnosis and prognosis and achieving a better response to therapy. This review focuses on recent studies on the biological and molecular mechanisms of response and resistance to treatment in BC.

BC

According to the International Agency for Research on Cancer, particularly the GLOBOCAN program, 2.1 million cases of BC were estimated in 2018 compared with 12.7 million in 2008,^{1,3} accounting for nearly one in four cancer cases in women.⁴ This increase in incidence may be explained by the growth and aging of the world population and the adoption of cancer-promoting lifestyles.

The development of molecular techniques, such as RNA sequencing, has allowed the determination of gene expression profiles, identification of tumor heterogeneity, and molecular classification of BC. Thus, six subtypes have been proposed based on the expression of ER, PR, estrogen-associated genes (*ESR1*, *GATA3*, *FOXA1*), and genes associated with the induction of proliferation, such as *HER2* and other genes located in the region of the *HER2* amplicon on chromosome 17.⁵ These six subtypes include the following: luminal A and luminal B, which are ER+ tumors, with expression of epithelial markers; HER2 + or HER2 enriched tumors, which show overexpression of the *HER2* gene; normal-like, with an expression profile that is similar to non-cancerous breast tissue; basal-like/triple negative BC (TNBC), which are characterized by lack of expression of ER, PR and HER2; and claudin-low, which is enriched in epithelial-to-mesenchymal transition (EMT) features.⁶ Some authors only consider five of the six breast cancer subtypes mentioned above and exclude the low claudin subtype.

Treatment of BC

BC is a heterogeneous disease in which each patient has individual characteristics, which has led to the search for new markers to improve not only the diagnosis but also the prognosis and to achieve a better treatment response. Currently, strategies for the treatment of BC depend on the tumor subtype, and the selected treatments are directed to specific targets that are functionally altered in each subtype. For example, endocrine therapy is used for tumors with positive hormone receptors (ER and PR) (luminal A and luminal B),^{7,8} however, some patients also require chemotherapy. For HER2+ tumors (luminal B and HER2+), treatment involves the use of monoclonal antibodies that recognize the extracellular domain of HER2 (trastuzumab) and inhibitors of the tyrosine kinase domain of HER2 (such as lapatinib), or even RNAi-mediated silencing,⁹ as well as endocrine therapy in cases with positive hormone receptors. Although chemotherapy is usually only given for TNBC, several molecular targets are being explored for this BC subtype, including epidermal growth factor receptor (EGFR), androgen receptor (AR), poly (ADP-ribose) polymerase (PARP), and vascular endothelial growth factor (VEGF).

Generally, conventional therapeutic treatments for the management of BC patients have included endocrine therapy, targeted therapy and chemotherapy (Figure 1). However, in recent years, other treatments have been explored, including cyclin-dependent kinase 4/6 (CDK4/6) inhibitors, microRNAs (miRNAs), immunotherapy, clustered regularly interspaced short palindromic repeats (CRISPR), tyrosine kinase inhibitors (TKIs), nanotechnological approaches, drug repurposing, and electrochemotherapy (ECT) (Figure 1). These new strategies may offer additional benefits to conventional treatments in terms of overcoming resistance and decreasing side effects.

Resistance and Overcoming Resistance in ER+ BC

Standard therapy for the treatment of ER+ BC is typically based on the use of endocrine therapy. This therapy includes the use of selective ER modulators, such as tamoxifen (TAM),¹⁰ selective ER downregulators (fulvestrant, FUL), and aromatase inhibitors (AIs)¹¹ (Figure 1). Additional treatments include CDK4/6 inhibitors,¹² PI3K inhibitors, and drug repurposing.

Endocrine Therapy

TAM

TAM is a non-steroidal anti-estrogen with partial estrogen-agonist activity that is widely used in the treatment of ER

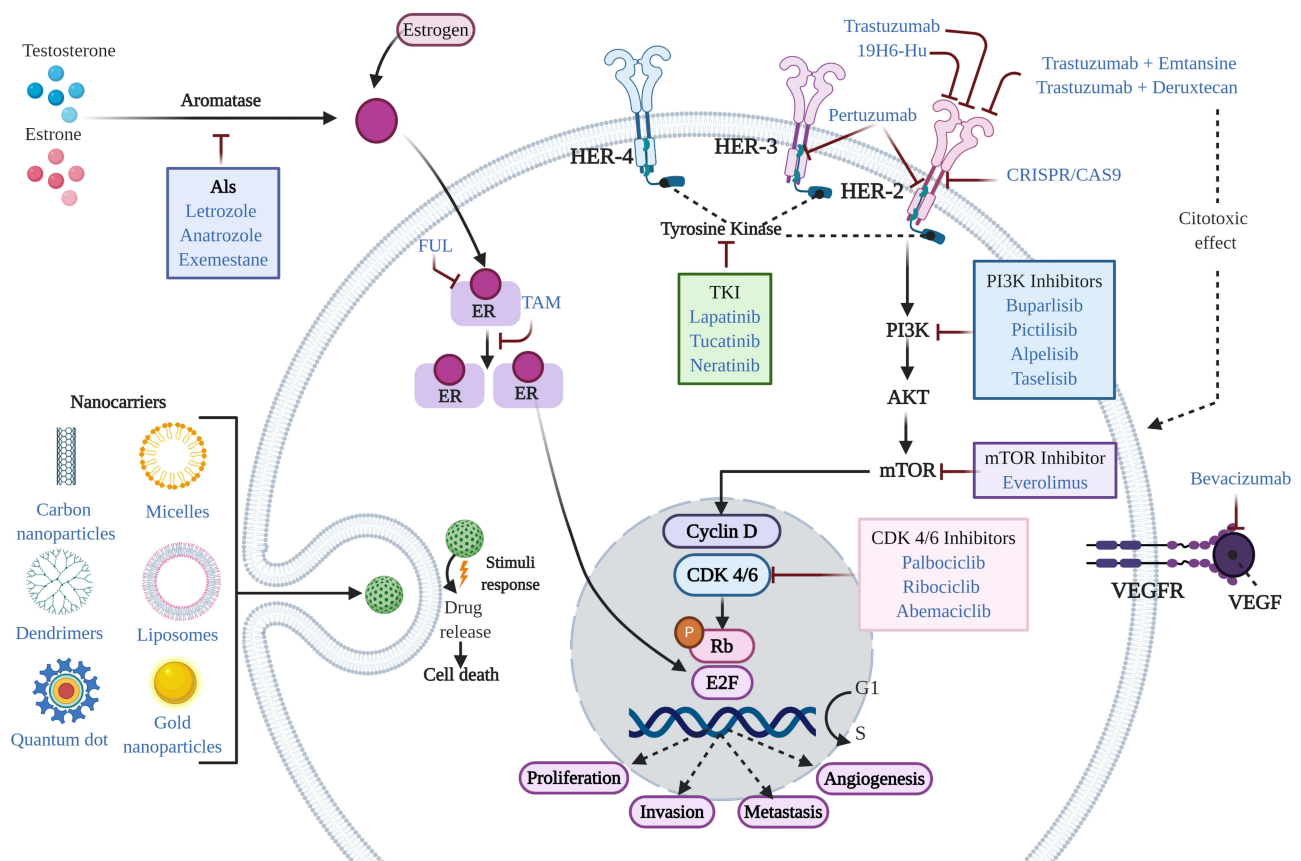


Figure 1 Mechanism of action of agents used in the treatment of BC. In general, conventional therapeutic treatments for the management of BC patients include endocrine therapy, targeted therapy, and chemotherapy. Standard therapy for the treatment of ER+ BC is typically based on the use of endocrine therapy (TAM, FUL, and Als). Additional treatments include CDK4/6 inhibitors, PI3K inhibitors, and drug repurposing. Treatments approved for HER2+ BC include humanized antibodies (trastuzumab, pertuzumab, and 19H6-Hu), PI3K inhibitors, antibody-drug conjugates (trastuzumab emtansine and trastuzumab deruxtecan), TKI inhibitors, mTOR inhibitors, nanotechnology approaches (nanocarriers), and CRISPR. Treatments for TNBC include chemotherapy and immunotherapy (bevacizumab), among others.

Abbreviations: BC, breast cancer; ER, estrogen receptor; TAM, tamoxifen; FUL, fulvestrant; Als, aromatase inhibitors; CDK4/6, cyclin-dependent kinase 4/6; PI3K, phosphatidylinositol 3-kinase; TKI, tyrosine kinase inhibitor; mTOR, mammalian target of rapamycin; CRISPR, clustered regularly interspaced short palindromic repeats; TNBC, triple negative breast cancer.

+ BC (Figure 1).^{13,14} Although patients with ER- tumors do not typically respond to these treatments, studies have shown that between 5% and 10% of these patients still benefit from therapy with TAM.^{13,15,16} The response to TAM is often of limited duration, suggesting that patients treated with TAM develop resistance over time.^{17,18} However, the mechanism through which this resistance occurs remains unknown. Several studies in patients with BC in the metastatic phase have reported that although >50% of patients with ER+ BC respond to TAM therapy, 40% of patients receiving TAM as adjuvant therapy eventually relapse and die from their illness.¹⁷ Resistance is thus the main problem with endocrine therapy.

Although endocrine therapy with TAM has been highly successful, 20%–30% of patients develop therapeutic resistance.^{14,17,19} Several mechanisms have been suggested that can lead to the development of resistance to endocrine

therapy and include genetic and epigenetic factors.^{20,21} Among the main mechanisms leading to TAM resistance are:

Estrogen Receptor 1 (ESR1) Gene Mutations

Mutations in the *ESR1* gene have been associated with acquired resistance from prolonged exposure to endocrine therapy with anti-estrogens.²² The specific point mutations in *ESR1* that are associated with resistance lead to the loss of ER expression and the development of resistance to treatment.²³ Such modifications cause further proliferation and tumor progression in the absence of hormonal stimulation.²³

Disruptions in TAM Metabolism

One of the molecular mechanisms underlying the resistance to endocrine therapy involves polymorphisms in cytochrome P450 family 2 subfamily D member 6

(*CYP2D6*), a member of the cytochrome P450 family that converts TAM into active metabolites (4-hydroxy tamoxifen-4OH-TAM). Such polymorphisms lead to the expression of enzymes with different levels of activity that result in reduced responses to TAM.²⁴ (Figure 2A)

Alterations in Translation Signals

Alterations in translation signals lead to increased expression and activity of the tyrosine kinase family receptors, such as human EGFR, insulin-like growth factor 1 receptor (IGFR), and G protein-coupled estrogen receptor (GPR30).²⁵ These events result in aberrant activation of cyclic adenosine monophosphate/protein kinase A (cAMP/PKA), mitogen-activated protein kinase (MAPK/ERK), and phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) signaling pathways.²⁶ Activation of these kinases leads to phosphorylation of ER and its co-activators such as collagen-binding A-domains of integrins (A1B1), mediator complex subunit 1 (MED1), or the coactivator-associated arginine methyltransferase 1 (CARM1), leading

to the activation of proliferation and inhibition of apoptosis.²⁷ (Figure 2B).

ER Gene Expression

In endocrine resistance, expression of factors such as fork head box protein A1 (FOXA1) and PBX homeobox 1 (PBX1) is often altered, leading to the altered or aberrant expression of ER²⁸ (Figure 2C). ER deregulation increases not only HER2-mediated signaling but also the activation of transcription factors such as SP1, AP-1, and nuclear factor kappa B (NFκB), which promotes the transcription of oncogenes.²⁹

Activation of Alternate Signaling Pathways

Other mechanisms that can lead to TAM resistance include the activation of alternative signaling pathways that prevent and/or exceed blocking of estrogen signaling induced by TAM. For example, mutations in the tumor suppressor protein, phosphatase and tensin homolog (PTEN), leads into uncontrolled transduction of the PI3K signal in ER⁺ tumors,

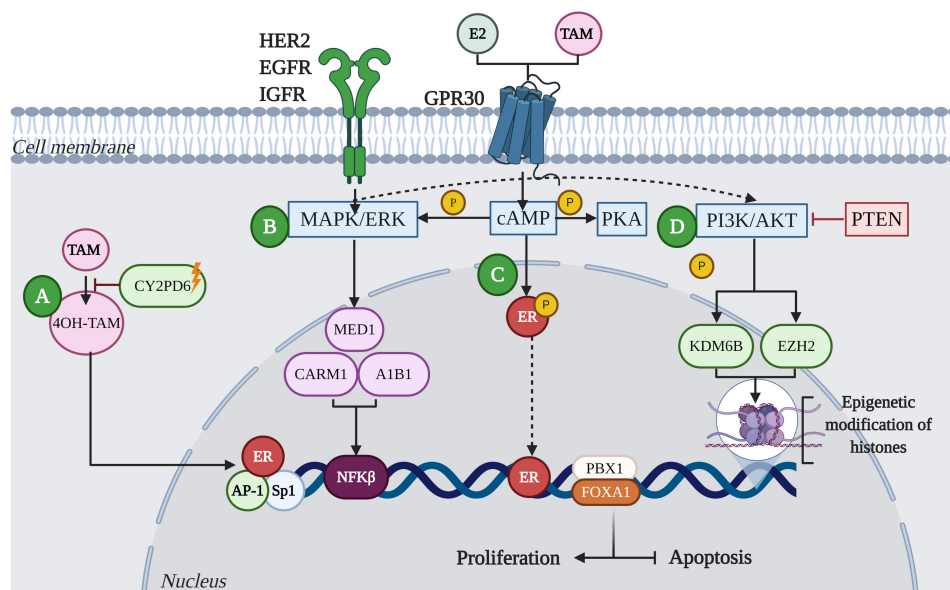


Figure 2 Mechanisms of resistance to endocrine therapy with tamoxifen (TAM) in breast cancer. **(A)** Resistance in BC is characterized by the deficiency of *CYP2D6*, which reduces the metabolism of 4OH-TAM. **(B)** Acquired resistance to TAM involves alterations in translation signals by increasing the expression and activity of tyrosine kinase receptor family proteins, such as HER2, EGFR, IGFR and GPR30. These events lead to aberrant activation of cAMP/PKA, MAPK/ERK and PI3K/AKT signaling pathways. Activation of these kinase pathways can result in phosphorylation of ER and its co-activators such as A1B1, MED1, or CARM1, leading to the activation of proliferation and inhibition of apoptosis. **(C)** Deregulation of ER increases not only HER2-mediated signaling, but the activation of transcription factors such as Sp1, AP-1 and NFκB, promoting oncogene transcription. Likewise, factors such as FOXA1 and PBX1 can recruit ER to specific genomic sites. **(D)** Other mechanisms that can lead to resistance to TAM involve the activation of alternate signaling pathways; for example, mutations in the tumor suppressor protein, PTEN, has been shown to increase phosphorylation of PI3K/AKT in ER⁺ tumors, leading to therapeutic resistance. Additionally, aberrant phosphorylation of proteins that modify histones, such as KDM6B and EZH2, can lead to resistance to endocrine therapy from the reactivation of genes.

Abbreviations: ER, estrogen receptor; *CYP2D6*, cytochrome P450 family 2 subfamily D member 6; 4OH-TAM, 4-hydroxy tamoxifen; HER2, human epidermal growth factor 2; EGFR, epidermal growth factor receptor; IGFR, insulin-like growth factor 1 receptor; GPR30, G protein-coupled estrogen receptor; cAMP/PKA, cyclic adenosine monophosphate/protein kinase A; MAPK/ERK, mitogen-activated protein kinase; AKT, protein kinase B; A1B1, collagen-binding A-domains of integrins; MED1, mediator complex subunit 1; CARM1, coactivator-associated arginine methyltransferase 1; PTEN, phosphatase and tensin homolog; KDM6B, lysine demethylase 6B; EZH2, enhancer of zeste 2 polycomb repressive complex 2 subunit; SPI, Sp1 transcription factor; API, AP-1 transcription factor; NFκB, nuclear factor kappa B; FOXA1, fork head box protein A1; PBX1, PBX homeobox 1.

leading to treatment resistance^{30,31} (Figure 2D). Alternatively, tumors can acquire TAM resistance through the regulation of AKT.³² Additionally, tumor cells can achieve resistance by decreasing the concentration of active TAM through the metabolism of an altered TAM.²¹ Furthermore, activation of PI3K/AKT pathway causes phosphorylation of demethyltransferase proteins [lysine demethylase 6B (KDM6B)] and methyltransferase proteins [similar to enhancer of zeste 2 polycomb repressive complex 2 subunit (EZH2)], which modify histones; this epigenetic mechanism leads to the development of endocrine therapy resistance from the reactivation of genes (Figure 2D).

FUL

FUL is an ER+ regulator with low cytotoxicity that, contrary to TAM, acts as an antagonist by binding, blocking and degrading ER and inhibiting ER transcriptional activity³³ (Figure 1). Therefore, its action is more powerful than that of TAM.³⁴ FUL has recently been approved for use in combination with Piqray (alpelisib),³⁵ which acts as a selective inhibitor of PI3K.³⁶ The effectiveness of this combination therapy (FUL + Piqray) was determined in the SOLAR-1 trial, in which postmenopausal women and men with advanced or metastatic BC with ER+/PR+/HER2- and mutations in the *PIK3CA* gene who were treated with the combination showed significantly prolonged progression-free survival.³⁷

AIs

AIs are one of the major treatment options for ER+ BC in postmenopausal patients. AIs stop estrogen production in postmenopausal women by blocking the aromatase enzyme, which converts androgen hormone to small amounts of estrogen. Anastrozole, exemestane and letrozole are AIs that are used in all clinical stages of BC worldwide (Figure 1). Anastrozole and letrozole are non-steroidal AIs, while exemestane is a steroidal AI.³⁸ Although these three compounds have been shown to suppress overall plasma and tissue estrogens by >90%, some studies suggest that letrozole is the most potent of the nonsteroidal compounds.³⁹

In metastatic BC, these AIs can be used sequentially and cause new responses in selected patients after resistance to the first treatment. For example, metastatic BC patients can benefit from a steroidal AI (exemestane) when they relapse after initial treatment with a non-steroidal AI (anastrozole or letrozole).^{39–41} However, information about the benefit of using a non-steroidal AI after a steroid AI is scarce.

Based on the results in metastatic BC after progression with anastrozole or letrozole therapy, treatment with exemestane alone or in combination with an mTOR inhibitor such as everolimus has been recommended.³⁸

CDK4/6 Inhibitors

The addition of CDK4/6 inhibitors to standard endocrine therapy has improved outcomes in first and last line therapy settings.¹² CDK4/6 inhibitors are anticancer drugs that have been mainly investigated in the last decade. The anti-carcinogenic effect of CDK4/6 inhibitors is based on their ability to block the progression of the cell cycle from G1 phase to S phase through blocking the activity of the cyclin D-CDK4/6 holoenzyme, thus limiting the proliferation of sensitive tumor cells.⁴² Currently, three selective CDK4/6 inhibitors, palbociclib, ribociclib, and abemaciclib, have been approved by the Food and Drug Administration (FDA) for use in the treatment of ER+/HER2- BC⁴³ (Figure 1). The use of these inhibitors in combination with AI as first-line therapy or with FUL as second-line therapy in ER+/HER2- metastatic BC has shown improved progression-free survival in Phase III trials.^{12,44,45} However, abemaciclib is the only inhibitor among the three CDK4/6 inhibitors that has received FDA approval as monotherapy in ER+/HER2- metastatic BC, indicating its high potential as a single agent.^{46,47}

Several phase III trials, such as the PALOMA-3 trial (FUL + palbociclib/placebo),⁴⁸ the MONARCH-2 trial (FUL + abemaciclib/placebo),⁴⁴ and the MONALEESA-3 trial (FUL with or without ribociclib),⁴⁹ have demonstrated the efficacy of the combination of FUL and CDK4/6 inhibitors. In the PALOMA-3 trial, the addition of palbociclib to FUL resulted in a prolongation of overall survival of 6.9 months among patients with advanced ER+/HER2- BC who showed disease progression after prior endocrine therapy.⁵⁰ In the MONARCH-2 and MONALEESA-3 clinical trials, the combination of FUL with abemaciclib or ribociclib, respectively, resulted in an improvement in both progression-free survival and overall survival.^{50,51}

Despite the benefits of CDK4/6 inhibitors, some adverse effects have been observed, including hematological toxicities, mainly neutropenia, and non-hematological toxicities such as fatigue, nausea, vomiting, stomatitis, alopecia, skin rash, diarrhea, decreased appetite, and infections. However, such toxicities are uncomplicated and manageable with dose interruption or reduction.⁵²

Recent studies have also shown that CDK4/6 inhibitors have similar efficacy when combined with an AI in the

first-line treatment of ER+ metastatic BC and are superior to monotherapy with FUL or AI, regardless of tumor characteristics.¹² These findings confirm that CDK4/6 inhibitors improve survival outcomes for ER+ BC patients when incorporated with AI in both the first and last lines.⁴⁷

PI3K Inhibitors

The PI3K/AKT/mammalian target of rapamycin (mTOR) pathway has been demonstrated to be involved in secondary endocrine resistance in ER+ BC,⁵³ and thus inhibition of this pathway is a promising approach to overcome resistance. Therapeutic blocking of this signaling pathway includes the use of PI3K inhibitors (PI3Ki) such as pan-PI3K inhibitors, which include buparlisib and pictilisib⁵⁴ (Figure 1). Buparlisib is an orally available pan-PI3Ki and the most clinically advanced agent in this class. The efficacy of this PI3Ki has been confirmed in several clinical trials (NCT01339442, NCT01610284), in which the combination of buparlisib with FUL in ER+ BC patients increased prolonged progression-free survival compared with FUL alone.⁵⁵ Pictilisib is an oral pan-PI3Ki of multiple PI3K isoforms. The combination of pictilisib and FUL in patients with postmenopausal metastatic BC previously treated with an AI was evaluated in a randomized Phase II clinical trial (FERGI, NCT01437566). The trial results showed no significant difference in progression-free survival with FUL + pictilisib compared with FUL + placebo. According to the authors, such results could be due to the higher toxicity from the combination treatment, including rash, diarrhea, transaminitis, and fatigue, which limits the administered dose of pictilisib.⁵⁶ Based on the above results, the development of pictilisib in this setting was discontinued. Additionally, the mTOR inhibitor everolimus (Afinitor) (Figure 1) overcomes resistance to hormone therapy by controlling the AKT/mTOR signaling pathway.⁵⁷ Furthermore, recent studies showed the benefit of everolimus with CDK4/6 inhibitor treatment in ER+ metastatic BC patients.⁵⁸

Drug Repurposing

Drug reuse or repositioning refers to the process of seeking new medical treatments within available medications, rather than developing new medications.⁵⁹ This strategy reduces the approval time for drug use and increases the success of clinical development. One example of a drug that has been repurposed for BC treatment is raloxifene, which has been used for the treatment and prevention of postmenopausal

osteoporosis. Raloxifene was approved by the FDA in 2010 for the primary chemoprevention of BC,⁶⁰ and one study showed that raloxifene was as effective as TAM in reducing the risk of BC.⁶¹ In fact, raloxifene was associated with a reduced risk of invasive BC in postmenopausal women.⁶² Other repurposed drugs with possible anticancer activity in BC are listed in Table 1.

In addition, anticancer activity have also been evidenced with the use of metformin, which is used for the treatment of type II diabetes; aspirin, an anti-coagulant,⁶³ clopidogrel, which is used for post-myocardial infarction;⁶⁴ and fingolimod, a drug for multiple sclerosis.⁶⁵ Although repurposed drugs have shown more benefits than conventional treatments, some professionals oppose the use of repurposed drugs.⁶⁶ However, numerous studies have demonstrated the efficiency and effectiveness of repurposed drugs in reducing resistance and toxicity in patients, especially drug combinations of reused drugs and conventional drugs for BC.

Resistance and Overcoming Resistance in HER2+ BC

Drugs approved for the treatment of HER2+ BC include humanized antibodies, PI3K inhibitors, antibody-drug conjugates (ADCs), and TKIs. Additionally, several drugs for the treatment of HER2+ BC, including ADCs, are currently being reviewed by the FDA for possible approval.

Humanized Monoclonal Antibodies (mAbs)

Currently available humanized antibodies for the treatment of HER2+ BC include trastuzumab, pertuzumab, and 19H6-Hu.

Trastuzumab

Trastuzumab specifically binds to the extracellular domain of HER2 to prevent the antibody-dependent cellular cytotoxicity,^{67–69} inhibiting the downstream signaling of HER2⁷⁰ and negatively regulating HER2^{49,71,72} (Figure 1). The introduction of trastuzumab to therapeutic regimens for patients with HER2+ BC has improved both the response and clinical outcome of these patients. However, not all patients with HER2+ BC respond to treatment and some develop resistance. The mechanisms related to resistance to trastuzumab therapy include the truncated form of HER2 (P95HER2),⁷³ masking by epitopes,^{74,75} activation of the PI3K/AKT/mTOR signaling pathway,⁷⁶ and FCGR2a polymorphisms,⁷⁷ among others.

Table I Some Repurposed Drugs for Breast Cancer Treatment

Type of Breast Cancer	Drug	Main Indication	References
ER+	Atrial Natriuretic Peptide	Heart failure	[142,143]
	Clarithromycin	Bacterial infections	[144]
	Cimetidine	Inhibits the production of acid in the stomach, histamine H2 receptor antagonist	[69]
	Melatonin	Insomnia	[145]
	Metformin	Anti-diabetic	[146]
ER-	Mefloquine	Malaria	[147]
	Azithromycin	Bacterial infection	[148]
	Digitoxin	Congestive heart failure, atrial fibrillation, atrial flutter, paroxysmal atrial tachycardia, cardiogenic shock	[149]
	Hydralazine	Hypertension	[150]
HER2+	Ethacrynic Acid	Diuretic	[151]
	Minocycline	Antibiotic	[152]
	Sirolimus	Inhibits organ transplant rejection	[153]
	Vardenafil	Erectile dysfunction	[154]
	Propranolol	Hypertension	[154]
TNBC	Lidocaine	Anesthetic	[155]
	Bepidil	Hypertension and chronic stable angina	[156]
	Carglumic Acid	Hyperammonemia from N-acetyl glutamate synthase deficiency	[157]
	Deferasirox	Acute iron intoxication, chronic iron overload	[158]
	Esomeprazole	Antacid	[159]
TNBC and HER2+	Artesunate	Malaria	[160]
	Atenolol	Hypertension, angina pectoris	[161]

Abbreviations: ER+, estrogen receptor positive; ER-, estrogen receptor negative; TNBC, triple negative breast cancer.

Truncated HER2 (p95HER2)

In some BC patients, the HER2 protein (185 kDa) gradually loses its extracellular domain through proteolytic detachment and the remaining 95 kDa fragment (p95HER2) associated with the membrane acquires constitutive activity.⁷⁸ The p95HER2 truncated form of HER2 lacks the extracellular domain, which is the binding site for trastuzumab; however, because the intracellular domain is intact (which shows strong kinase activity), some studies have associated p150 HER2 with clinical resistance to trastuzumab.⁷³ Compared with tumors expressing the full-length HER2, p95HER2-expressing tumors have worse prognosis and are at an increased risk of metastasis.⁷³

Masking by Epitopes

A mechanism of obstruction of the connection point between trastuzumab and HER2 corresponds to the masking of epitopes, with proteins Mucin 4 (MUC 4) and hyaluronic complex polymer (CD44) being involved in this mechanism.⁷⁴ When MUC4 and CD44 are active, they

alter the HER2 binding point,^{74,75} leading to a decrease in trastuzumab binding by 20%.⁷⁵

Activation of the PI3K/AKT/mTOR Pathway

The PI3K signaling pathway plays a crucial role in growth and cell survival. Somatic missense mutations in the *PIK3CA* gene are common in patients with HER2+ BC.⁷⁶ In addition to contributing to neoplastic transformation,²⁶ these mutations lead to alterations in the PI3K/AKT/mTOR pathway and reduced efficacy of trastuzumab therapy. Therefore, additional diagnostic testing for planning customized treatment, such as detecting *PIK3CA* gene mutations, have recently been approved and are used to establish personalized therapies.⁷⁹

FCGR1Ia Polymorphisms

Immune effector cells, such as natural killer cells or macrophages, can recognize and bind trastuzumab through their receptors. Some of the receptors, called Fc-gamma receptors, including FCGR1Ia, seem to be crucial for the clinical

response to trastuzumab. Thus, the presence of polymorphisms in these receptors can modulate the response to trastuzumab and result in the development of resistance.⁷⁷

Pertuzumab

Pertuzumab is a second-generation recombinant humanized monoclonal antibody that binds to the extracellular dimerization domain II of HER2, preventing its heterodimerization with HER1, HER3, HER4 and IGF-1R31,⁸⁰ and thus inhibiting cell proliferation (Figure 1). Pertuzumab has been associated with both increased progression-free survival for patients with metastatic BC⁸¹ and better outcomes for patients with early BC. However, in patients with non-visceral metastases or small primary tumors with negative nodes, the therapeutic benefit of pertuzumab is relatively small.⁸²

19H6-Hu

Based on the low response rates of BC patients to trastuzumab therapy, new treatment strategies were explored. The new anti-HER2 antibody (19H6-Hu), which enhances the anti-tumor efficacy of trastuzumab and pertuzumab with a distinct mechanism of action, has shown promising efficacy. 19H6-Hu is a novel humanized anti-HER2 monoclonal antibody that binds to the HER2 extracellular domain with high affinity (Figure 1) and inhibited the proliferation of multiple HER2+ BC cell lines as a single agent or in combination with trastuzumab. One study showed that 19H6-Hu in combination with trastuzumab was more effective at blocking phosphorylation of ERK1/2, AKT (S473) and HER2 (Y1248) in HER2+ BC cells compared with trastuzumab alone or in combination with pertuzumab.⁸³

PI3K Inhibitors

PI3K inhibitors are used in combination with AIs for the treatment of metastatic BC.⁸⁴ However, most PI3K inhibitors are more toxic than beneficial. The FDA approved more selective, less toxic, and more effective inhibitors for the treatment of metastatic BC in patients with *PIK3CA* gene mutation, such as alpelisib and taselesib⁸⁵ (Figure 1). Additionally, another study reported that PI3K/AKT/mTOR inhibitors in combination with trastuzumab or trastuzumab and paclitaxel were efficient and safe for patients and showed beneficial anti-tumor activities.⁸⁶

ADCs

ADCs are a means of delivering cytotoxic drugs specifically to cancer cells. The mechanism of action of ADCs involves the delivery and subsequent internalization of the

ADC and the release of highly active, free cytotoxic agents into cancer cells, ultimately leading to cell death. ADCs used in the treatment of advanced BC include trastuzumab emtansine (T-DM1)⁸⁷ and trastuzumab deruxtecan⁸⁸ (Figure 1). T-DM1 is a conjugate of trastuzumab and a cytotoxic drug (DM1, derived from maytansine) that is effective and generally well tolerated when administered as a single agent. The efficacy of this ADC has been demonstrated in randomized trials.⁸⁹ Although the superior efficacy of T-DM1 compared with trastuzumab or trastuzumab plus chemotherapy has been reported in the treatment of metastatic BC, most patients treated with T-DM1 eventually show disease progression,⁸⁷ and some HER2+ BCs do not respond or only respond minimally to T-DM1.⁸⁷ One study showed that altered traffic/metabolism of T-DM1 is one of the predominant mechanisms associated with resistance to T-DM1, and a greater understanding of such mechanisms is necessary to develop strategies to overcome T-DM1 resistance.⁹⁰

Another ADC used in the treatment of BC is trastuzumab deruxtecan. This conjugate comprises an anti-HER2 antibody, a cleavable tetrapeptide-based linker, and a cytotoxic topoisomerase I inhibitor. Although the use of this ADC in a pretreated patient population with HER2+ metastatic BC showed durable antitumor activity, the efficacy of this ADC in HER2+ metastatic BC patients previously treated with TDM-1 needs to be confirmed.⁸⁸ Trastuzumab deruxtecan is also being evaluated for the treatment of metastatic BC in patients with low HER2 expression, for whom current available therapies targeting HER2 are ineffective. The results of trastuzumab deruxtecan treatment in these patients have shown a response rate of 44.2%.⁹¹

Currently, several HER2-directed ADCs are under clinical investigation for both HER2 amplified and HER2 expressing but not amplified BCs, including ARX788 and XMT-1522. ARX788, a novel next-generation anti-HER2 ADC containing an anti-HER2 monoclonal antibody site-specifically conjugated to amberstatin,^{92,93} has shown anti-tumor effects and rapid tumor regression in murine xenograft models of the HER2+ BC cell lines BT474 and HCC1954.⁹² Furthermore, ARX788 showed a stronger inhibitory effect than T-DM1 on T-DM1-responsive BC cells and caused complete tumor regression in a trastuzumab-resistant BC xenograft model derived from JIMT-1 cells.⁹⁴ Two Phase 1 trials on ARX-788 (clinicaltrials.gov identifiers: NCT02512237 and NCT03255070) are ongoing but the results have not yet been published.⁹⁵ XMT-1522 is a ADC

containing a human IgG1 anti-HER2 monoclonal antibody (HT-19) that binds to domain IV of HER2 to an epitope that is distinct from the trastuzumab binding site.⁹⁶ Notably, the HT-19 antibody does not compete with trastuzumab or pertuzumab for binding to HER2.⁹⁷ Clinical studies on a panel of 25 tumor cell lines differentially expressing HER2 showed that XMT-1522 was more potent than T-DM1 in inhibiting cell proliferation.⁹⁷ Additionally, in a HER2 BC BT474 xenograft model and a patient-derived HER2 xenograft model, treatment with XMT-1522 induced complete tumor regression at doses of 2 mg/kg and 1 mg/kg, respectively.⁹⁷ Benefits of XMT-1522 therapy were also observed in a BC xenograft model, in which a significant inhibition of tumor growth was observed.⁹⁸ Antitumor efficacy, with complete response, was also observed in some mice after the combined treatment of XMT-1522 with the anti-PD1 monoclonal antibody; the response was better when the two drugs were administered sequentially (XMT-1522 followed by anti-PD1 monoclonal antibody).⁹⁵ The use of XMT-1522 is currently being investigated in patients with advanced BC expressing HER2 progressing on standard therapy (clinicaltrials.gov identifier: NCT02952729).

Other ADCs currently under preclinical and clinical research for the treatment of BC include A166, ALT-P7, DHES0815A, DS-8201a, RC48, SYD985, and MEDI4276. However, to the best of our knowledge, there are no published data available for A166, ALT-P7, and DHES0815A at the time of writing.

TKIs

TKIs used to treat HER2+ BC include lapatinib, neratinib, and tucatinib (Figure 1). Lapatinib, a potent and reversible small molecule TKI that binds both HER2 and EGFR, inhibits the growth of trastuzumab-resistant HER2+ tumor cells.⁹⁹ Neratinib, an irreversible small-molecule TKI of HER1, HER2 and HER4,¹⁰⁰ has been shown to be effective as a single agent in the treatment of HER2+ metastatic BC pretreated with trastuzumab.¹⁰¹

Tucatinib is an investigational, oral TKI that is highly selective for the kinase domain of HER2 with minimal inhibition of EGFR.¹⁰² Combinations between tucatinib and monoclonal antibodies (such as trastuzumab) have been recently developed for the treatment of HER2+ metastatic BC patients. For instance, a non-randomized open-label phase 1b study found that the combination of tucatinib with trastuzumab and capecitabine showed encouraging antitumor activity in patients with HER2+ BC, including those with brain metastases. However, side effects

such as diarrhea, nausea, palmo-plantar erythrodysesthesia syndrome, fatigue, and vomiting were observed.¹⁰³ Additionally, in heavily pretreated patients with HER2+ metastatic BC, the combination of tucatinib plus trastuzumab and capecitabine resulted in better progression-free survival and overall survival outcomes.¹⁰⁴

Resistance and Overcoming Resistance in TNBC

Treatment of TNBC mainly involves the use of chemotherapy. Additionally, given the immunogenicity of TNBC, this type of cancer can respond to immunotherapy. New therapeutic options are currently being developed for this disease, including ECT, androgen antagonists such as bicalutamide and abiraterone acetate,¹⁰⁵ and nanosomal docetaxel lipid suspension (NDLS)-based chemotherapy.¹⁰⁶

Chemotherapy

Despite the associated short- and long-term risks, chemotherapy remains essential to prevent recurrence in many patients with advanced BC. Chemotherapy is the only systemic therapy with proven efficacy in TNBC and an important complement to endocrine therapy or HER2-targeted therapy in patients with hormone receptor-positive (ER+ and PR+) BC.² In fact, the first-line implementation of taxanes has been associated with optimization of the immune status of BC patients and therefore with a good clinical response. Optimization of immune status has been associated with increased activity of natural killer and lymphokine-activated killer cells, with increased levels of interleukin-6 (IL-6) and reduced levels of IL-1 and tumor necrosis factor.¹⁰⁷ Chemotherapeutics include the use of alkylating agents, antimetabolites, anti-tumor antibiotics, topoisomerase inhibitors, TKIs, and mitotic inhibitors.¹⁰⁸

Resistance to chemotherapy is a result of chronic exposure to chemotherapy and increases the chances of recurrence and accelerated metastasis.¹⁰⁹ Therefore, resistance is a major limitation for the successful treatment of BC. However, the exact mechanisms leading to such resistance remain unclear.¹¹⁰ Several mechanisms associated with the resistance to chemotherapy are described below.

Membrane Glycoproteins That Act as Effusion Pumps

Membrane glycoproteins that act as effusion pumps are ATP hydrolysis-dependent proteins that actively transport different substrates across the cell membrane. The ATP-dependent transporters or ABC transporters (ATP-binding cassette) include multidrug resistance proteins (MRP) such

as the permeability glycoprotein (P-GP). These transport proteins are involved in the most widely recognized drug resistance mechanism.¹¹¹ However, recent studies show that FUL reverses resistance to doxorubicin (DOX) mediated by glycoprotein transporters in hormone receptor-negative BC cells. The reversal of resistance occurs through the sensitization of tumor cells potentiating DOX cytotoxicity by increased intracellular drug, and further activation of apoptosis and cell cycle arrest³⁴ (Figure 3A).

Receptor Affinity

The amount and affinity of receptors present in the membrane determine the effectiveness of the drug, allowing it to be paired or not (Figure 3B).

Enzyme System That Deactivates Anticancer Drugs

The enzyme system involved in the deactivation of anti-cancer drugs, and therefore involved in the process of drug

resistance,^{111,112} includes multi-drug resistance gene (*MDR1*) and glutathione S transferase Pi (GSTP1). While GSTP1 decreases the concentration and the effective life of drugs, resulting in drug inefficiency,¹¹³ *MDR1* gene is significantly overexpressed in multidrug resistance phenotype¹¹⁴ (Figure 3C).

Epigenetic Mechanisms

Epigenetic mechanisms, such as DNA methylation and histone modifications, play a key role in the regulation of gene expression (silencing of tumor suppressor genes and/or overexpression of oncogenes)^{110,115} (Figure 3D). Alterations in epigenetic mechanism have not only been associated with the acquisition of resistance but are also involved in tumor progression and metastasis.¹⁰⁹ The application of epigenetic therapies, such as hydralazine and valproic acid, has been reported to achieve a significant reversal of acquired resistance to chemotherapy.¹¹⁰ In fact, it has been indicated that

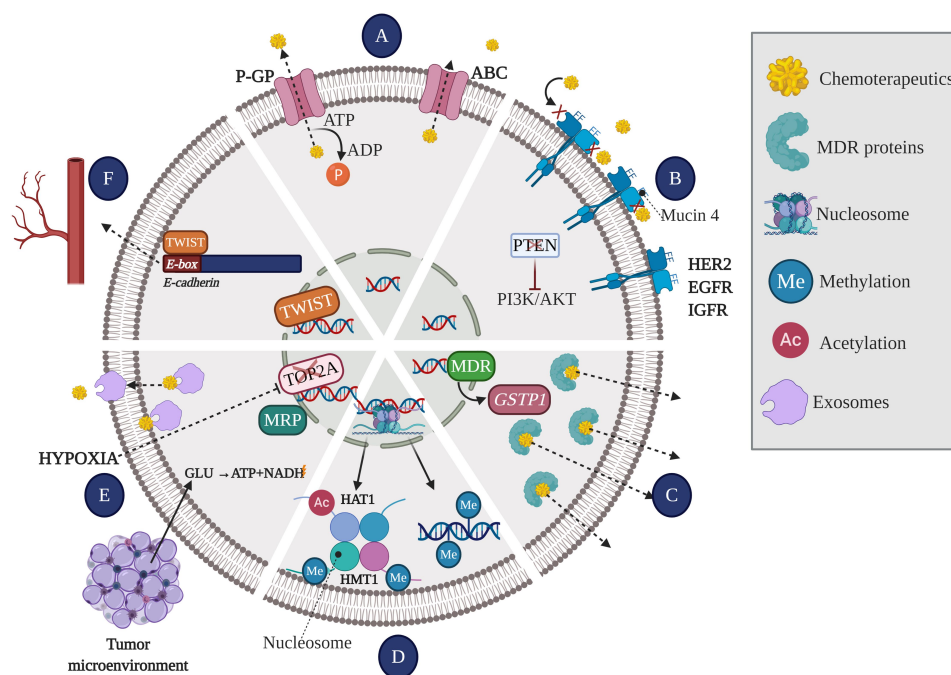


Figure 3 Mechanisms leading to the generation of resistance to chemotherapy. (A) Effusion pumps: Membrane glycoproteins act as pumps extracting the drug efflux of intracellular space, thus reducing drug concentration and efficacy. (B) Receptor affinity: The number and affinity of receptors present on the membrane determine the effectiveness of the drug, allowing it to be paired or not. (C) The enzyme system involved in the deactivation of anti-cancer drugs, and therefore involved in the process of drug resistance, includes multi-drug resistance gene (*MDR1*) and glutathione S transferase Pi (GSTP1). While GSTP1 decreases the concentration and the effective life of drugs, resulting in drug inefficiency, *MDR1* gene is significantly overexpressed in multidrug resistance phenotype. (D) Epigenetic mechanisms: DNA methylation and histone modifications [acetylation (Ac) or methylation (Me)] lead to the silencing of tumor suppressor genes and/or overexpression of oncogenes. (E) Tumor microenvironment: the tumor microenvironment creates the optimal niche for the development of cancer cells. In conditions such as hypoxia, cancer cells interact with stromal and immune system cells through exosomes from which they acquire nutrients to use other metabolic pathways, leading to the overexpression of the MRP and deactivating and extracting the drug from inside the cell. Additionally, hypoxia is a trigger for tumor resistance to chemotherapy, since it leads to both decreased DNA topoisomerase II alpha (*TOP2A*) expression and upregulation of MRP. (F) Angiogenesis: The TWIST1 transcription factor can recognize the E-box gene sequence on the promoter of *E-cadherin* and depress its transcription, thereby leading to decreased cell adhesion and promoting angiogenesis.

Abbreviations: P-GP, permeability glycoprotein; ABC, ATP-dependent transporters; PTEN, phosphatase and tensin homolog; PI3K/AKT, phosphatidylinositol 3-kinase/protein kinase B; HER2, human epidermal growth factor 2; EGFR, epidermal growth factor receptor; IGFR, insulin-like growth factor I receptor; MDR, multi-drug resistance; GSTP1, glutathione S transferase Pi; HAT1, histone acetyltransferase I; HMT1, histone methyltransferase I; TOP2A, DNA topoisomerase II alpha; MRP, multidrug resistance protein; TWIST1, twist family bHLH transcription factor; GLU, glutamate; ATP, adenosine triphosphate; NADH, nicotinamide adenine dinucleotide (NAD) + hydrogen (H).

the molecular effects exerted by valproic acid and hydralazine include the inhibition of histone deacetylases, the demethylation of DNA and the reactivation of genes in primary tumors of patients with BC, increasing the efficacy of chemotherapy.¹¹⁶

Tumor Microenvironment

The tumor microenvironment includes stromal cells (fibroblasts, vascular cells, and immune system cells), soluble factors (such as growth factors, transcription factors, hormones, and cytokines), extracellular matrix, signaling molecules, hypoxia (which facilitates the release of exosomes), and mechanical signals (exosomes).^{109,117} In addition to creating favorable niches for metastasis, these factors facilitate the transfer miRNA, cytokines, and P-GP from resistant cells, altering the gene expression of sensitive cells, thereby increasing their survival.^{112,117,118} Tumors are usually exposed to hypoxic conditions; therefore, to obtain energy, they must rely on glycolysis, which turns chemotherapeutic drugs ineffective by the increased expression of metabolic enzymes. In fact, Tsuruo et al¹¹⁹ reported that hypoxia is a trigger for tumor resistance to chemotherapy, since it leads to both decreased DNA topoisomerase II alpha (*TOP2A*) expression and upregulation of MRP expression (Figure 3E).

Angiogenesis

The twist family bHLH transcription factor 1 (TWIST1) plays a key role in angiogenesis. TWIST1 positively regulates EMT,¹⁰⁹ invasion, and metastasis.¹¹⁸ The TWIST1 transcription factor can recognize the E-box gene sequence on the promoters of *E-cadherin* and depress its transcription, thereby leading to decreased cell adhesion and promoting angiogenesis.¹¹³ In addition, was reported that up-regulation of *TWIST1* by NF- κ B contributes to the chemoresistance^{113,115} (Figure 3F).

Pharmacokinetics

Pharmacokinetics are associated with the reduction of intracellular drug accumulation because of increased drug efflux, causing the generation of reactive oxygen species and detoxification mediated by exosomes.^{110,112,120} Pharmacodynamics may confer chemoresistance because it leads to alterations of the drug target,¹¹⁰ repression of tumor suppressor genes, impaired DNA damage repair, acquisition of characteristics similar to cancer stem cells, cellular changes induced by EMT for angiogenesis, and tumor microenvironment conditions.¹¹³ The significant reduction in survival rates for repeated relapse patients is

the most concerning issue associated with pharmacokinetics.

Resistance to Treatment with Anthracyclines: DOX

Anthracyclines, such as DOX, are one of the most widely used drugs in the treatment of metastatic BC as a single-agent therapy. Anthracyclines are DNA damaging agents and inhibit TOP2A. DOX intercalates into DNA, preventing TOP2A binding and causing replication fork blockage,¹¹⁷ which eventually leads to apoptosis.¹⁰ DOX is used as the first-line treatment in BC and primarily for the treatment of advanced BC with an overall response rate of 30%–50%,¹²⁰ alone or in combination therapy with paclitaxel,¹¹⁰ docetaxel (DOC), cyclophosphamide, 5-fluorouracil, trifluridine, or vorinostat. Despite its extensive use, DOX is an antitumor drug with high cytotoxicity.¹¹⁰ The cardiotoxicity mechanisms of DOX remain to be explained; however, formation of DNA adducts and free radicals have been reported as potential mechanisms.¹²⁰

Diverse hypotheses have been formulated around DOX resistance, including resistance related to BC tumor subtypes,¹²¹ resistance related to the altered expression of specific proteins, including NF κ B and small modifier proteins like ubiquitin (SUMO), and resistance related to epigenetic modifications. High levels of IL-6, IL-8, IL-1 β , transforming growth factor beta (TGF- β), and the prion protein (PrPc) have also been associated with resistance to DOX.¹¹⁷

Resistance to Treatment with Taxanes: Docetaxel (DOC)

DOC is an antineoplastic agent; its mechanism of action involves inhibiting cell division by stabilizing microtubules, inhibiting tubulin depolymerization, and killing tumor cells.¹⁰⁸ DOC is one of the most active drugs available for the treatment of metastatic BC.¹²² DOC is systematically applied in patients who do not respond or develop resistance to chemotherapy with anthracyclines (such as DOX).^{3,108} The risks and long-term benefits of chemotherapy are poorly understood because many studies do not report long-term results or do not monitor therapeutic resistance.¹²⁰ However, in recent prospective trials on neoadjuvant chemotherapy, taxanes along with anthracyclines have been observed to increase life expectancy by metastasis-free survival in more aggressive tumors.¹¹⁸

Resistance to DOC has been mainly associated with miRNA transport and membrane glycoproteins via exosomes, which also promotes high drug efflux from the cell

interior to the exterior.¹¹² DOC resistance is highly influenced by the presence of cytokines. For example, IL-8 leads to increased NF κ B and is involved in the activation of survival pathways such as those mediated by tumor necrosis factor receptor 2 (TNFR2), whereas high levels of IL-17A lead to increased cell proliferation and thus resistance.¹¹⁷

Immunotherapy

Considering that TNBC has the highest frequency of mutations and therefore the highest possibility of expressing immunogenic neoantigens, this BC subtype is considered to have the highest probability of responding to immunotherapy.¹²³ Cancer immunotherapy aims to overcome the ability of tumor cells to resist the endogenous immune response by stimulating the patient's immune system. Immunotherapy mainly involves the use of mAbs that are selectively directed to a specific target involved in tumor cell proliferation.¹²⁴ Among the mAbs used in BC, the synthetic antigen sialyl-Tn has been proven to be safe and highly efficient because it triggers a large immune response.¹²⁵

Other mAbs include bevacizumab, an antibody that inhibits the activation of VEGF receptor, thereby increasing the rate of drug response and progression-free survival. Other mAbs, such as aflibercept (a recombinant fusion protein) and pazopanib (a TKI) have shown good results in the inhibition of BC tumor cell migration and metastasis. Some mAbs substantially improve the effects of DOX in tumor cells expressing high levels of EGFR.¹²⁶

In recent years, anti-PD-1 receptor antibodies have been considered incredibly promising in the field of cancer immunotherapy. The PD-1 receptor and its ligands PD-L1/PD-L2 belong to the family of immune control proteins and act as co-inhibitory factors to modulate the response of T cells and to prevent chronic autoimmune inflammation.^{126,127} Anti-PD-1 mAbs (such as pembrolizumab and nivolumab), which are known as immune checkpoint inhibitors, block the PD-1 receptor or PD-L1 and PD-L2 ligands expressed by cancer cells and prevent their binding; this leads to an inhibition of the immune modulatory signal and allows T cells to remain active against tumors. However, a limited efficacy of these mAbs (targeting PD-1 and PD-L1) has been reported, mainly owing to the induction of apoptosis in patients with metastatic BC because of the low proportion of lymphocytes in infiltrating tumors. Therefore, a combination of immunotherapy and targeted therapies such as angiogenesis inhibitors is used for BC patients.^{126,127}

ECT

ECT was developed as a treatment option for TNBC patients, given the absence of viable therapeutic targets in this BC subtype. ECT involves the efficient delivery of natural bioactive molecules with anti-cancer effects via a biophysical means and is based on the combined use of electroporation together with chemotherapy drugs to increase absorption. Recent research has demonstrated the efficacy of ECT and showed that ECT can dramatically increase the intracellular concentration and cytotoxicity of several FDA-approved drugs, such as bleomycin and cisplatin, leading to a complete tumor response with minimal drug doses.¹²⁸ Additional studies in BC cell lines showed that ECT increased the cytotoxicity of curcumin treatment by 7-fold,¹²⁹ increased apoptosis in MDA-MB-231 cells, and minimally affected the viability of non-cancerous MCF10A cells.^{129,130} A recent study demonstrated the anticancer effects of ECT against the MDA-MB-231 cell line, which is representative of the TNBC subtype.¹³¹ These effects include the suppression of key proteins involved in the proliferation, differentiation, migration, survival, and apoptosis of cancer cells.

Emerging Treatments

In recent years, emerging treatments are being developed that could offer additional benefits to conventional treatments that are mainly related to overcoming resistance and decreased side effects. These treatments involve nanotechnological approaches (Figure 1), CRISPR, exosomes, and miRNAs.

Nanotechnological Approaches

Nanotechnological approaches are being developed to minimize the toxicity in healthy tissues generated by targeted therapy while maintaining the efficacy of the treatments. These approaches are based on a nanoparticle delivery system (nanocarriers) that increases the drug-site contact time and the elimination time and reduces the resistance to the drug. Examples of nanocarriers in BC therapy include nanoparticles, polymeric micelles, dendrimers, carbon nanotubes, liposomes, and quantum dots^{107,112,113} (Figure 1).

The NDLS-based chemotherapy system was recently developed. NDLS is a new formulation of lipid-based, polysorbate 80 and ethanol-free formulation of docetaxel developed to overcome toxicity problems.¹³² The function of NDLS is based on its ability to infiltrate and become entrapped in the damaged tumor vasculature and collagen

material of necrotic tumor tissue, leading to increased drug retention (leading to an enhanced permeability and retention effect).¹⁰⁶ NDLS showed comparable efficacy and tolerability to conventional DOC in the treatment of metastatic BC in both prospective and retrospective studies.¹³² A recent study demonstrated that NDLS-based chemotherapy was effective and well tolerated in the treatment of patients with BC in all settings (neoadjuvant, adjuvant, and metastatic).¹⁰⁶ The efficacy of NDLS is currently being prospectively evaluated in patients with TNBC (ClinicalTrials.gov identifier: NCT03671044).

CRISPR

Given the wide variety of morphological and molecular features of tumor cells, the identification of new therapeutic targets to prolong survival and limit the acquisition of resistance in patients with BC is crucial. Implementation of genomics edition by CRISPR system has provided a glimpse of broad cellular heterogeneity and the opportunity to act on tumor cells with mutant alleles,^{133,134} such as alterations in *EGFR*, *KRAS*, *BAP1*, *BRAF*, *BRCA1*, and *BRCA2*, or with replicative immortality without affecting normal cells.^{133,135} The CRISPR system (CRISPR/Cas9) has been established in preclinical trials as an effective tool to specifically attack and/or resensitize tumor cells.¹³⁶

Potential targets have been identified in BC through CRISPR/Cas9, including microtubule affinity regulating

kinase 4 (MARK4) and fermitin family homolog-2 (FERMT2), which are related to metastasis; microtubule-associated serine/threonine kinase (MASTL), which is involved in cell proliferation; the tyrosine protein kinase FYN that is involved in drug resistance; and cyclin-dependent kinase 7 (CDK7), which is negatively associated with tumor size and grade.¹³⁵ CRISPR/Cas9 has also been used to generate changes in exons of the *HER2* gene. Such changes lead to the expression of a truncated HER2 protein that prevents dimerization of the transmembrane domain, leading to inhibition of signaling pathways such as MAPK/ERK and PI3K/AKT, as well as cell proliferation and tumorigenicity.¹³⁴ As with immunotherapy, CRISPR/Cas9 can also target stromal cells in the tumor microenvironment to generate mutations in VEGF and VEGFR2, thereby inhibiting stromal cell migration activity.¹³⁶

Exosomes

Exosomes, an important class of extracellular vesicles, transport and distribute biological macromolecules, such as proteins, nucleic acids, and anti-tumor drugs, and are considered promising therapeutic strategies for targeted drug delivery in BC.¹³⁷ The therapeutic potential of exosomes as nano-transporters of DOX has been considered as a strategy to overcome resistance to chemotherapy.¹³⁸ The use of exosomes could allow the targeted administration of drugs,

Table 2 miRNAs in the Response to Breast Cancer Therapy

miRNA	Target	Effect	References
miRNA-129-5p	<i>MDR</i>	Reverses MDR action	[162,163]
miR-200c	<i>TUBB3</i>	Restores paclitaxel chemosensitivity of cancer cells	[164,165]
	<i>ZEB1</i>		
	<i>ZEB2</i>		
miR-181c	<i>SPP1</i>	Affects the pathway of chemoresistance by mutant p53, restores chemosensitivity to doxorubicin in breast cancer, and inhibits endothelial-mesenchymal transition	[166]
miR-218r	<i>BRCA1</i>	Regulates chemosensitivity to cisplatin	[167–169]
miRNA-221/222	<i>ER</i> <i>CDKN1B</i>	Decreases resistance to tamoxifen	[124,167,169–172]
miRNA-342-3p			
miRNA-873			
Let-7b/Let-7i			
miR-520h	<i>PTEN</i>	Inhibits apoptosis induced by paclitaxel	[173]

Abbreviations: MDR, multi-drug resistance; *TUBB3*, class III beta-tubulin; *ZEB1*, zinc finger E-box binding homeobox 1; *ZEB2*, zinc finger E-box binding homeobox 2; *SPP1*, secreted phosphoprotein 1; *BRCA1*, BRCA1 DNA repair associated; *CDKN1B*, cyclin dependent kinase inhibitor 1B; *PTEN*, phosphatase and tensin homolog.

overcoming several limitations associated with conventional nanoparticles, including cytotoxicity, drug modification, greater synergistic effects, and biocompatibility, among others.^{107,112,113}

miRNAs

Several miRNAs have been identified as biomarkers for prognosis and treatment planning in BC.¹³⁹ miRNAs also play a crucial role in the regulation of BC cell sensitivity to chemotherapy.^{140,141} For example, miR326 and miR-451 negatively regulate the expression of *MDR* genes, including *MDR-1*, to overcome resistance. *MDR-1*, which encodes the P-GP transporter, multi-drug resistance proteins (MRPs), and the BC resistance protein (BCRP), which transport both hydrophilic and hydrophobic substrates, are particularly important for chemotherapy.¹¹¹ Over 80% of the currently used anticancer agents are transported by P-GP, and thus its overexpression can lead to multi-drug resistance.¹¹³ Several reports have identified miRNAs that play important functions in BC (Table 2).

Conclusions

Cancer is a common disease and represents one of the biggest health problems in the world, with BC being the leading cause of cancer death in women. One of the most significant clinical problems in the treatment of BC is the development of drug resistance. Therefore, the identification of the possible biological and molecular mechanisms involved in such resistance could help the development of new therapeutic targets. Recent research has shown that the application of combined therapies and use of emerging therapies may be effective for overcoming resistance and minimizing side effects, respectively.

Acknowledgments

We thank the Universidad del Rosario for the payment of the edition and publication of the article. The authors also thank Gabrielle White Wolf, PhD, from Edanz Group (<https://en-author-services.edanzgroup.com/ac>) for editing a draft of this manuscript.

Disclosure

The authors report no conflicts of interest in this work.

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