

Molecular Biology Mechanisms and Emerging Therapeutics of Triple-Negative Breast Cancer

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Abstract: Triple-negative breast cancer (TNBC) is an aggressive subtype of breast cancer that is conventionally characterized by the absence of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (HER2), accounting for approximately 15–20% of all breast cancers. Compared to other molecular phenotypes, TNBC is typically associated with high malignancy and poor prognosis. Cytotoxic agents have been the mainstay of treatment for the past few decades due to the lack of definitive targets and limited therapeutic interventions. However, recent developments have demonstrated that TNBC has peculiar molecular classifications and biomarkers, which provide the possibility of evolving treatment from basic cytotoxic chemotherapy to an expanding domain of targeted therapies. This review presents a framework for understanding the current clinical experience surrounding molecular biology mechanisms in TNBC (Figure 1). Including immunotherapy, polymerase (PARP) and PI3K/AKT pathway inhibitors, antibody-drug conjugates, and androgen receptor (AR) blockade. Additionally, the role of miRNA therapeutics targeting TNBC and potential strategies targeting cancer stem cells (CSCs) are discussed and highlighted. As more and more treatments arise on the horizon, we believe that patients with TNBC will have a new sense of hope.

Keywords: triple-negative breast cancer, PI3K/AKT pathway inhibitors, antibody-drug conjugates, cancer stem cells, miRNA therapeutics

Introduction

Breast cancer has emerged as the most prevalent malignancy and is one of the principal causes of cancer-related fatalities in recent years. According to the World Health Organization, it is estimated that by 2022, one out of every eight women will suffer from breast cancer.^{1–4} Breast cancer is a complex disease that can be classified into three major tumor subtypes - hormone receptor (HR) positive, HER2-enriched, and triple-negative, based on the expression of estrogen and progesterone receptors and HER2 amplification. With the rapid advancements in medical technology, newer insights and a better understanding of the disease have emerged. The histopathological differentiation of breast cancer demands that we consider these subtypes as distinct entities and use tumor molecular signatures in clinical decision-making to guide the appropriate treatment.^{5–7}

Triple-negative breast cancer (TNBC) is characterized by the absence of hormone receptors and human epidermal growth factor. As the lethal subtype of breast cancer, it accounts for approximately 15% of all cases, demonstrating unique clinical and molecular characteristics.^{8,9} Epidemiological data indicates that TNBC is more commonly diagnosed in younger women, has a shorter time to relapse in the early stages, and carries a higher risk for hepatic, pulmonary, and central nervous system metastasis.^{10–12} Within five years of diagnosis, the mortality rate for TNBC patients is 40%, but for those who experience recurrence within three months, the mortality rate can reach 75%.^{13,14}

In terms of pathology, TNBC predominantly presents with high-grade and high proliferation rates, particularly in invasive ductal carcinoma NOS, metaplastic carcinoma, apocrine carcinoma, and medullary carcinoma, illustrating its favorable response to chemotherapy with cytotoxic-based drugs. Additionally, some rare histological subtypes such as

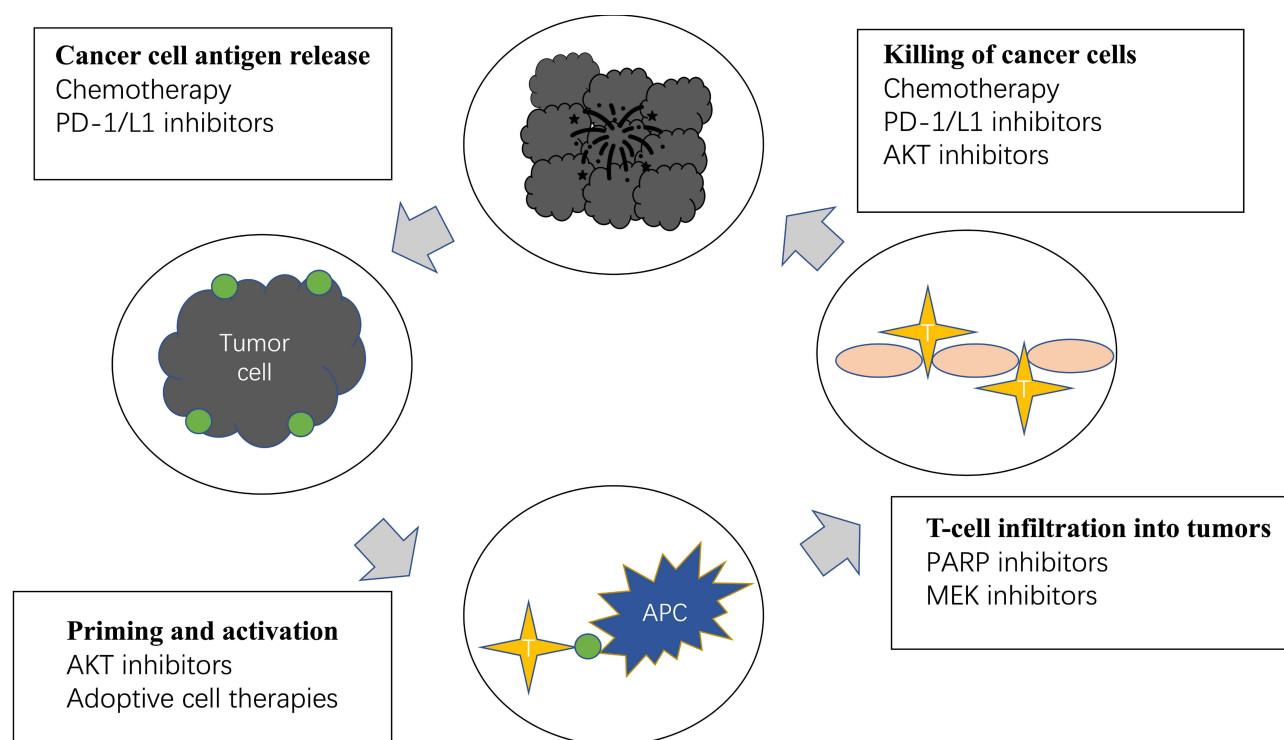


Figure 1 Current immunotherapy and combination therapeutic strategies for the treatment of triple-negative breast include killing of cancer cells, prevent cancer cell antigen release, promote T-cell infiltration into tumors and activate immune system. The main agents include chemotherapy, PD-1/L1 inhibitors, AKT inhibitors, PARP inhibitors and MEK inhibitors.

adenoid-cystic carcinoma, secretory carcinoma, adenomyoepithelioma, polymorphous carcinoma, and mucoepidermoid carcinoma are low-grade neoplasms.^{15,16} Therefore, conventional postoperative adjuvant chemoradiotherapy may not be adequate, and residual metastatic lesions can lead to tumor recurrence.⁷ Taken together these breast cancer subtypes demonstrate that the TNBC family is heterogeneous and intricate, opening new frontiers for innovative prognostic therapies for TNBC.

Currently, chemotherapy remains the primary systemic treatment option for both early and advanced stages of the disease due to its special molecular phenotype. However, the residual metastatic lesions that result from adjuvant chemoradiotherapy may eventually lead to tumor recurrence. As a result, there is an urgent to develop innovative ideas and directions for the treatment of TNBC, including novel treatment regimens and targets.

Diagnosis

As we know, it is the integral diagnosis and typing of TNBC tumors is the initial step in establishing personalized, targeted medications for each TNBC individual. At present, TNBC is predominantly diagnosed through imaging and immunohistochemistry (IHC).¹⁷ The major methods of breast imaging include mammogram, breast ultrasound, and magnetic resonance imaging (MRI). Mammography can identify breast cancer at an early stage by analyzing distribution, size, morphology, and microcalcifications. However, the positive predictive value of mammography needs to be enhanced, which can affect the judgment of doctors.¹⁸ Ultrasound is widely used in evaluating of lumps, which could detect small breast cancers that may not be visible on mammography. Currently, the BIRADS-US classification system is extensively applied in categorizing focal breast lesions.¹⁹ Additionally, the outcomes of a large clinical trial revealed that adding MRI to mammography improve the rate of cancer detection in high-risk breast cancer patients, but it also increased false-positive findings.²⁰

IHC is typically used for staining cells with biomarkers, including hormone receptors and HER2 markers, to type breast carcinoma. The American Society of Clinical Oncology (ASCO) and the College of American Pathologists (CAP)

have been provided approximately 126 latest guidelines to enhance reliability, reproducibility, and reduce false-negative results from IHC testing.^{21,22}

Furthermore, several promising strategies have been presented for future TNBC diagnosis such as positron emission tomography (PET), nano biosensor, and circulating tumor nucleic acids (ctNAs), which could diagnosis TNBC in real-time, precisely, and minimally invasive ways.²³

Molecular Characteristics of TNBC

In recent years, there have been significant developments made in illustrating the gene expression patterns and molecular subtypes of TNBC, which have potential therapeutic associations.^{24,25} Moreover, methylome sequencing of The Cancer Genome Atlas (TCGA) samples has identified biologically distinct subsets within TNBC that respond differently to standard chemotherapy and novel targeted agents.

Molecular Subtypes

Traditionally, breast carcinomas were divided into 18 different subtypes based on their morphological characteristics. However, since 2001, molecular characteristics have substituted morphological characteristics as the new approach to characterizing breast tumors.²⁶ Based on gene expression, the largest overall difference is observed between hormone receptor (HR)-positive and HR-negative tumors. The subtypes are now referred to as luminal A, luminal B, basal-like, HER2-positive and normal-like breast cancer, each associated with distinct prognoses and treatment possibilities.²⁶ Figure 2 shows the changes in breast cancer typing from 2010 to 2016.

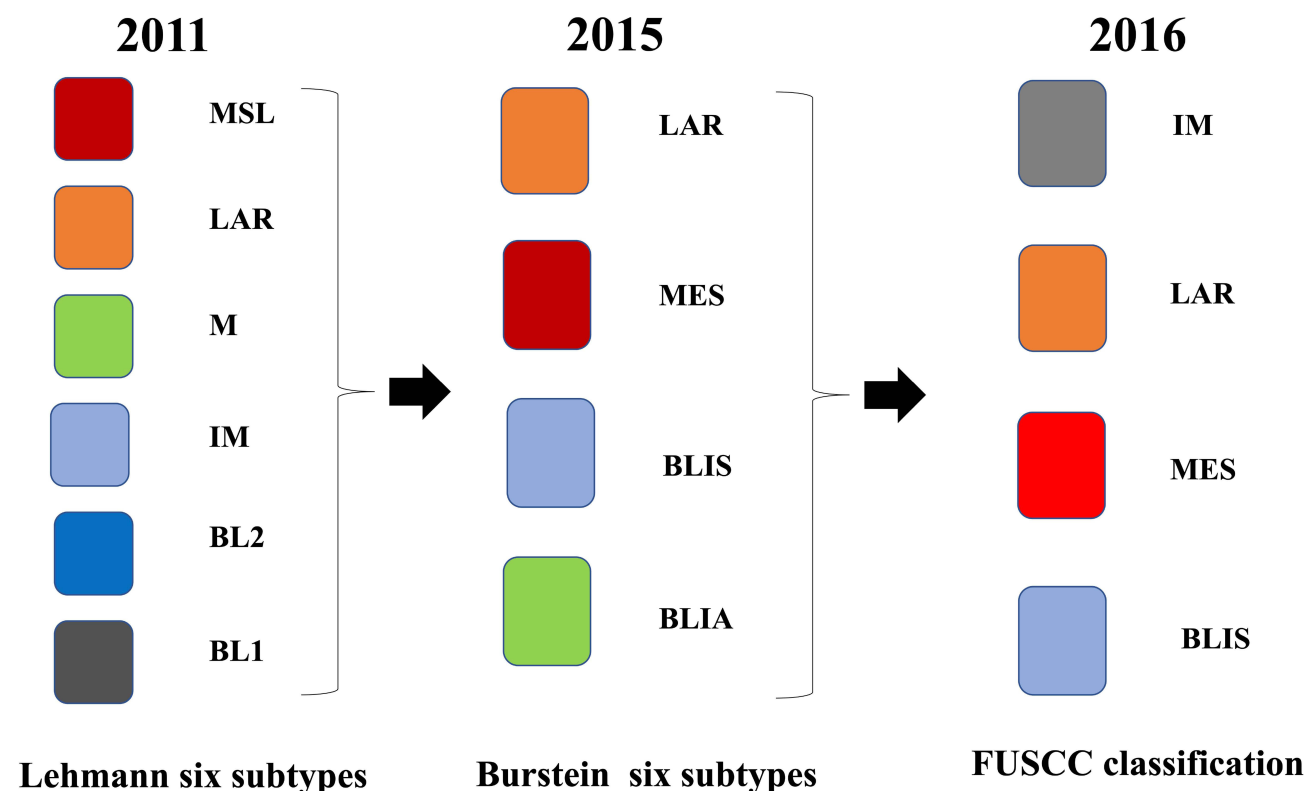


Figure 2 In 2011, Lehmann et al categorize TNBC into six different subtypes: basal-like 1 (BL1), basal-like 2 (BL2), mesenchymal (M), mesenchymal stem-like (MSL), immunomodulatory (IM), and luminal androgen receptor (LAR). In 2015, Burstein identified four distinct TNBC subtypes: luminal androgen receptor (LAR), mesenchymal (MES), basal-like immunosuppressed (BLIS), and basal-like immune-activated (BLIA). In 2016, Liu and colleagues developed a novel TNBC classification system that integrates the expression profiles of both mRNAs and lncRNAs. The system divided TNBC subtypes into four subtypes: immunomodulatory (IM), luminal androgen receptor (LAR), mesenchymal-like (MES), basal-like and immune suppressed (BLIS).

In 2011, Lehmann et al conducted a gene analysis of 21 breast cancer data sets, wherein they identified 587 TNBC cases. This helped them categorize TNBC into six different subtypes: basal-like 1 (BL1), basal-like 2 (BL2), mesenchymal (M), mesenchymal stem-like (MSL), immunomodulatory (IM), and luminal androgen receptor (LAR).²⁷

The BL1 subtype is typically characterized by heavy enrichments in cell division pathway components and DNA damage response pathways. There is some evidence indicating that BL1 patients may respond well to Poly (ADP-ribose) polymerase (PARP) inhibitors and genotoxic agents.²⁸ In contrast, the BL2 subtype has high activations in growth factor signaling, glycolysis, and the expression of myoepithelial markers. Potential targeted therapeutic drugs for BL2 subtype include mTOR inhibitors and growth factor inhibitors.²⁸

The M subtype is generally referred to as metaplastic breast cancer due to its tissue characteristics, which resemble sarcoma-like and squamous epithelial cells.²⁸ In addition, the high expression of cell migration-related signaling pathways, extracellular matrix–receptor interaction pathways, and differentiation pathways make M-subtype patients more sensitive to mTOR inhibitors and drugs targeting epithelial–mesenchymal transition.²⁹ Similarly, the MSL subtype also exhibits aberrant activation in cell differentiation pathways, epithelial to mesenchymal transition (EMT), transforming growth factor (TGF)-beta signaling pathway, and processes associated with growth factor signaling pathways. However, compared to the M subtype, the MSL subtype demonstrates lower levels of cell proliferation-related genes and higher levels of stemness-related genes. The potential targeted therapeutic drugs for both M subtype and MSL subtype patients include dasatinib and Abl/Src inhibitors.³⁰

The IM subtype exhibits distinct expressions in immune cell-associated genes, cytokine signaling, immune cell signaling, antigen processing and presentation, chemokine signaling pathway, and immune signal transduction pathway. Several studies have indicated that immune checkpoint inhibitors such as PD1, PDL1, CTLA-4 could be utilized for treating patients with IM subtype breast cancer.³¹

On the other hand, unlike other TNBC subtypes, the LAR subtype does not express ER receptors but displays high activation in hormonal-related signaling pathways, which involve androgen and estrogen metabolism, steroid hormone biosynthesis, porphyrin, and chlorophyll metabolism. As a result, the use of anti-AR therapy may well benefit patients with LAR-subtype breast cancer.³²

In 2015, Burstein and colleagues furthered the above molecular subtyping by identified and confirmed four distinct TNBC subtypes: luminal androgen receptor (LAR), mesenchymal (MES), basal-like immunosuppressed (BLIS), and basal-like immune-activated (BLIA). Through Spearman correlation analysis, these two classification systems were substantially associated with each other ($P=0.039$). Compared to Perou's "PAM50" TNBC molecular classification, this classification allows for distinct clinical prognoses and definition the clinical outcome of each subtype.³³

In 2016, considering the emerging significant role of long noncoding RNAs (lncRNAs) in cellular processes, Liu and colleagues developed a novel TNBC classification system that integrates the expression profiles of both mRNAs and lncRNAs. The system divided TNBC subtypes into four subtypes: immunomodulatory (IM), luminal androgen receptor (LAR), mesenchymal-like (MES), basal-like and immune suppressed (BLIS).³⁴

In concordance with the Lehmann/Pietenpol classification, the IM subtype predominantly exhibits immune cell process, such as cytokine-cytokine receptor interaction, T-cell receptor signaling pathway and B-cell receptor signaling pathway. The upregulated gene functions in this subtype are closely associated with immunity. In the LAR type, although immunohistochemical analysis has confirmed these tumors as TNBC, gene expression profiling has demonstrated significant elevations in androgen and estrogen metabolism, steroid hormone biosynthesis, porphyrin, and chlorophyll metabolism. This indicates that anti-androgen and anti-estrogen therapies could be effective.^{27,33} The MES subtype has enriched pathways, including extracellular matrix (ECM)-receptor interaction, focal adhesion, transforming growth factor (TGF)-beta signaling pathway, and low levels of genes related to cell proliferation. The MES subtype also exhibits enriched pathways in cell division and cell cycle-related pathways.

After analyzing the FUSCC classification system, it was revealed that the new subtype IM and LAR virtually identical to the Lehmann/Pietenpol IM and LAR types. Similarly, the new subtype BLIS predominantly contained the Lehmann/Pietenpol BL1 and M types. The new subtype MES contained all six of the Lehmann/Pietenpol subtypes, with the MSL and M subtypes being the most prevalent. Additionally, the novel TNBC classification system identified

subtype-specific lncRNAs that could potentially serve as biomarkers and treatment targets, facilitating patient counseling and individualize the treatment of TNBC.

Molecule Mutations

Apart from discussing the distinct molecular subtypes, another important aspect of TNBC molecular characteristics is the alteration status of *BRCA*. The data has reveals that the prevalence of *BRCA* mutations of TNBC is about 10–30%. Moreover, approximately 80% of breast cancers with *BRCA1* germline mutations are basal-like profile tumors.^{35,36} Additionally, studies have proved the association between deleterious *BRCA1* mutations and the risk of developing TNBC.³⁷ The loss or mutation of tumor suppressors *TP53*, *PTEN*, retinoblastoma gene (*RBI*) and the *KRAS* oncogene are more frequently lost or mutated in TNBC.^{38,39} The enhanced expression of Ki-67, vimentin, laminin and the low expression of *Bcl-2* are also distinguishing features of TNBC from other breast tumors.^{40,41} Virtually, TNBC is not essentially a homogeneous disease entity; instead, it may be seen more as a symptom than as an individual disease that comprises several types of cancers characterized by molecular profiles.

TNBC Cytotoxic Therapy and Efficacy Evaluation

Compared to other types of breast cancer, cytotoxic chemotherapy remains the mainstay of systemic treatment for TNBC. A substantial body of literature over the past two decades has demonstrated its significant advantage in the neoadjuvant, adjuvant and metastatic setting.⁴² The main reason for this is the absence of high-frequency molecular alterations and the limited number of known biomarkers, rendering specific endocrine therapies and targeted therapies ineffective for TNBC. In recent years, neoadjuvant chemotherapy regimens have increasingly been used in TNBC treatment,⁴³ with several studies highlighting its significantly higher pathological remission rates and significant enhancement of the prognosis for TNBC patients. Approximately 30–40% out of early-stage TNBC patients treated with standard neoadjuvant achieve a complete response (pCR) after treatment.⁴⁴ Some existing evidence suggests that in the neoadjuvant or adjuvant setting, using dose-dense and high-dose regimens and choosing taxanes and anthracyclines are more effective in TNBC patients.^{45–48} The NCCN Guidelines recommended the most active agents in the first-line setting using numerous lines of chemotherapy based on taxane, anthracycline, cyclophosphamide, cisplatin, and fluorouracil for TNBC patients. Despite the combination chemotherapy regimens at the expense of increased toxicity, the outcomes of TNBC patients have been studied to have higher response rates compared with single agents.⁴⁹ After considering the performance status, the risk of adverse events, prior chemotherapy regimens, disease burden, and patient preferences of chemotherapeutics, currently available chemotherapy regimens are adriamycin + cyclophosphamide + taxel (ACT), adriamycin + cyclophosphamide (AC), docetaxel + cyclophosphamide (TC), cyclophosphamide + methotrexate + fluorouracil (CMF), and cyclophosphamide + adriamycin + fluorouracil (CAF).⁵⁰ Therefore, choosing appropriate chemotherapy regimens, considering the specific posology and safety profile of each agent, is necessary to ensure adequate treatment outcomes and prognosis for TNBC patients.

Taxanes

As inhibitors of microtubules that can impede tumor angiogenesis, taxanes have been extensively utilized ever since their approval by the FDA in 1984 for the treatment of progressive ovarian carcinoma. Their use as an adjuvant in the treatment of early breast cancer marked a new era in the therapy, beginning in 1989.⁵¹ The primary target of taxanes is β -tubulin of polymerized microtubules, to which they bind with high affinity to hinder microtubule depolymerization and impair mitosis.⁵² Taxanes function in a complicated manner, regulating various processes and pathways in cancer biology, including apoptosis, mitosis, angiogenesis and ROS production.⁵³ Taxanes such as docetaxel and paclitaxel have exhibited a higher response rate for triple-negative breast cancers than for receptor- positive cancers.^{54–56} The US Oncology 9735 trial was the first randomized controlled trial to directly compare the efficacy of TC adjuvant regimens with AC adjuvant regimens in breast cancer patients. After a median of seven years of follow-up, the results revealed that four cycles of TC adjuvant regimens had overall survival rates comparable to standard AC adjuvant regimens, regardless of patient age, hormone receptor status, and lymph node status.⁵⁷

Anthracycline

Anthracyclines and anthracycline antibiotics have become essential components of adjuvant treatment and are considered among the most potent drugs in breast cancer therapy. The anti-tumor effect of anthracyclines is generally attributed to intercalate with DNA, which induces DNA damage through the generation of free radicals. However, it is noteworthy that their use is limited by cardiotoxicity at high cumulative doses and hematologic malignancies.⁵⁸ Based on a large number of clinical studies, the optimal dosing schedules of anthracycline adjuvant therapy for breast cancer are 60 mg/m² of doxorubicin and 100 mg/m² of epirubicin.⁵⁹ The MINDACT trial compared an anthracycline-based regimen to a non-anthracycline regimen. Despite both groups having comparable outcomes, the anthracycline-taxane regimen is superior in TNBC, so we continue to recommend it as an adjuvant anthracycline in higher-risk triple-negative disease.⁶⁰

Cyclophosphamide

As one of the most successful chemotherapy drugs, cyclophosphamide has been registered on the World Health Organizations List of Essential Medicines. It has been used to treat a range of cancers, including lymphomas, breast and ovarian cancers, both as a single agent and as adjuvant therapy.⁶¹ The primary antitumor mechanism of low dose cyclophosphamide is its ability to deplete the suppressive regulatory T cells (Tregs) population. This is a fundamental component of the tumor immune evasion arsenal that is correlated with tumor progression.^{62–64} Recently, docetaxel plus cyclophosphamide (TC) has been established as a standard adjuvant chemotherapy regimen for triple-negative operable breast cancer. In addition, a prospective study by Yokoyama et al evaluating the efficacy and safety of capecitabine + epirubicin + cyclophosphamide combination therapy (CEX) as neoadjuvant chemotherapy for 18 patients with HER-2-negative breast cancer reported positive results. All patients finished four cycles of CEX, and the total pathological complete response (pCR) rate was 50%, with virtually all the pCRs observed in TNBC patients. The findings highlight the effectiveness of this regimen in treating triple-negative breast cancer.⁶⁵

Capecitabine

As an orally administered prodrug of fluorouracil, capecitabine is preferentially metabolically activated preferentially at the tumor site, demonstrating its antineoplastic activity and synergizing with other cytotoxic agents, indicating potential as a component of first-line combination cytotoxic chemotherapy. Currently, in US and Europe, capecitabine combined with docetaxel is widely used for metastatic breast cancer treatment.⁶⁶ Results from the CREATE-X trial indicates that the safety and effectiveness of six to eight cycles of adjuvant capecitabine following standard anthracycline and taxane neoadjuvant chemotherapy in early TNBC with a residual tumor burden.⁶⁷ In addition, a meta-analysis of randomized controlled trials also suggested the possibility of improved disease-free survival and overall survival for TNBC patients following the addition of capecitabine to standard chemotherapy, though the known toxicity profile requires caution.⁶⁸

Platinum Agents

Platinum-based agents can cause DNA crosslink strand breaks, leading to apoptosis specifically in cells with dysfunctional repair pathways. The BLBC subtype, accounting for most TNBC tumors, is particularly sensitive to platinum-based agents due to genomic instability, BRCA1 abnormalities, and defective DNA repair pathway.^{69–71} Preclinical and clinical data has indicated that BRCA1 carriers treated with cisplatin in neoadjuvant chemotherapy exhibit high pCR rates, while metastatic BRCA1 carriers also respond well.^{72,73} Consistent with preclinical and recent clinical data, research examining the use of platinum-based chemotherapy for TNBC has shown modest efficacy. Subsequent clinical trials have demonstrated that platinum-based monotherapy can be particularly beneficial for BRCA1/2 mutation carriers.^{74–76}

Steven J. et al conducted a multicenter Phase II clinical trial of single-agent platinum for metastatic TNBC (TBCRC009) to evaluate its monotherapy by assessing biomarkers. The results showed that the overall response rate was 25.6%, with a response rate of 18.7% for carboplatin and 2.6% for cisplatin. Additionally, 54.5% of those who responded had BRCA1/2 mutations.⁷⁴ This research results suggest that platinum-based agents have particularly effective for TNBC.

Emerging Targeted Therapies in TNBC

As contemporary technology platforms have contributed to the understanding of the molecular diversity of TNBC, we have been able to identify promising therapeutic targets for TNBC patients. Currently, several tumor-driving signaling pathways targeted therapies in TNBC, including EGFR targeted therapy, VEGF targeted therapy and PI3K/AKT/mTOR targeted therapy in TNBC are under clinical investigation.

EGFR Targeted Therapy

Epidermal growth factor receptor (EGFR) is a receptor tyrosine kinase (RTK) that comprises of an extracellular ligand binding domain, a transmembrane domain, and a cytoplasmic tyrosine kinase domain. When a ligand binds to EGFR, its kinase activity is activated to participate in various downstream signaling pathways, promoting cell proliferation and motility. The EGFR gene overexpression is frequently observed in TNBC, making it a valid therapeutic target, particularly for BL2-subtype tumors.^{77,78} Inhibitors of EGFR including TKIs and mAbs, have already been developed and are currently available for use in the clinic, making it an attractive option for the treatment of TNBC patients.

EGFR TKIs, including gefitinib, erlotinib, afatinib, osimertinib and erlotinib, can restrain EGFR kinase activity by binding to the ATP binding site of the EGFR tyrosine kinase, and are currently approved for and highly effective against NSCLC.^{79,80} Several clinical trials have been conducted to investigate the toxicity and efficacy of TKIs in breast cancer. However, results have not demonstrated it to be an effective therapeutic for TNBC. For instance, a phase II clinical trial of gefitinib as a monotherapy in metastatic breast cancer concluded that gefitinib monotherapy at 500 mg daily was not exhibit efficacious to metastatic breast cancer patients.⁸¹ Another randomized phase II trial evaluated the effect of adding gefitinib to neoadjuvant EC, and showed a lack of significant difference in the outcomes of pathologic complete response (pCR) did not show a significant difference between patients treated with gefitinib and placebo. Nevertheless, the difference between TNBC and non-TNBC can be observed for gefitinib.⁸² Similarly, cetuximab appeared to have little activity as monotherapy, but the patient outcomes were enhanced when combined with carboplatin.⁸³ Although the data of clinical trials of EGFR inhibitors therapies have shown mixed results in TNBC, several EGFR-TKI clinical trials are ongoing, including TKI monotherapy and TKI in combination with chemotherapy.⁸⁴

VEGF Targeted Therapy

Vascular endothelial growth factor (VEGF) is the most significant angiogenic factor that promotes tumor cell proliferation and the formation of new vessels in breast cancer.⁸⁵ The level of VEGF is an independent factor related to poor prognosis. Patients with TNBC show significantly higher levels of VEGF and shorter recurrence-free survival and overall survival compared to non-TNBC patients.⁸⁶

Bevacizumab, a recombinant humanized monoclonal antibody against VEGF-A, was approved by the FDA in 2004 for use as part of combination therapy regimens to treat metastatic colorectal cancer. It is effectiveness and generally well-tolerated nature as a VEGF inhibitor making it promising as a single agent or as part of combination regimens for breast cancer, according to the results from clinical studies.⁸⁷ However, it is important to note that the addition of bevacizumab may increase the incidence of adverse events such as hypertension, neutropenia, and mucositis. Two large, randomized studies demonstrated a significant increase in the rate of pathological complete response in HER2-negative patients when bevacizumab was added to neoadjuvant chemotherapy, and the efficacy was restricted mainly to TNBC patients.^{88,89} The GeparQuinto trial also investigated the effect on pCR of adding bevacizumab to standard neoadjuvant chemotherapy, and the results showed a higher pCR rate in the bevacizumab arm, particularly in the BRCAg mutations patients. However, the outcome of the BEATRICE study did not show a significant improvement in disease-free or overall survival. The heterogeneity of TN tumors could be the reason for these divergent results, and bevacizumab may have different reactions to molecular subgroups.⁹⁰ In conclusion, bevacizumab shows promising potential as a positive function in metastatic TNBC. However, it still requires further follow-up to evaluate its potential effect.

PAM Targeted Therapy

The PI3K-Akt-mTOR (PAM) signaling pathway is known to play a crucial role in angiogenesis, tumor proliferation, and inhibition of apoptosis. The Cancer Genome Atlas (TCGA) has revealed significant mutation within the PI3K-Akt-mTOR (PAM) pathway in TNBC.^{5,91} Several preclinical studies also demonstrated that the PAM pathway was activated and upregulated in TNBC, and the M, MSL and BL subsets of TNBC showed sensitivity to PI3K/mTOR inhibitors.^{27,92} While these studies confirmed the PAM pathway is a promising therapeutic target, the implication of inhibitors in breast cancer are not yet well-defined.

The mTOR inhibitor, everolimus, has been approved for the treatment of metastatic breast cancer that is ER-positive and resistant to aromatase inhibitors.⁹³ However, data on its clinical efficacy for TNBC is limited. A neoadjuvant clinical trial was conducted to assess the effects of adding everolimus to paclitaxel and anthracycline in TNBC. The results showed that there was no statistically significant increase in pCR. Further investigation is required to determine the most effective combinations and the subgroup of patients that will respond positively mTOR inhibitors.⁹⁴

AKT is another critical node in the PAM signaling pathway, and some preclinical studies have demonstrated the antitumor activity of its inhibitors.^{95,96} Ipatasertib is a highly selective ATP-competitive AKT inhibitor. In the LOTUS phase II trial, the effectiveness of the combination of ipatasertib and paclitaxel in metastatic TNBC was evaluated. The results demonstrate the progression-free survival was longer when compared to paclitaxel alone. This is the first outcome suggesting the efficacy of AKT-targeted therapy for TNBC.⁹⁷ Another AKT inhibitor, capivasertib, has also shown very promising preliminary data in a phase II study, and a larger Phase III trial is ongoing to validate its efficacy.⁹⁷ More clinical trials are currently underway to further clarify the role of PAM-targeted therapy in the treatment of TNBC.

Upcoming Treatment Options

At present, there is no specific targeted agent approved by the FDA or EMA for the treatment of TNBC. However, in this article, we will discuss the most recent data on promising and novel targeted approaches for TNBC.

Immunotherapy

Immunotherapy is a promising treatment strategy for TNBC, with documented prolonged survival in other solid tumors. Immune checkpoint inhibitors (ICIs) have proven to be the most successful immunotherapeutic agents. These work by blocking immunosuppressive receptors and improving the cytotoxicity and proliferative capacity of tumor-infiltrating lymphocytes (TILs).^{98,99} Some of the popular monoclonal antibodies against PD-1, such as pembrolizumab, nivolumab, and against PD-L1 including atezolizumab, durvalumab, avelumab, along with ipilimumab against CTLA-4, have been observed to generate durable responses across various tumor types.^{100,101}

PARP Inhibitors

Polyadenosine diphosphate (ADP) ribose polymerase (PARP) is a highly conserved multifunctional enzyme that plays a significant role in the mechanism of single-strand DNA break repair. Its primary function of PARP is to facilitate DNA repair, cellular proliferation, and catalyzing the transfer of ADP-ribose from NAD⁺ to target proteins.¹⁰² The effects of PARP inhibitors result in the catalytic inhibition of PARP1 and locking PARP1 on damaged DNA to stall the progress of replication forks. In normal cells, damaged DNA sequences can be restored back to their native form by HR proteins. However, in tumor cells lacking HR proteins, such as BRCA1, BRCA2, PALB2, or RAD51 would use error-prone DNA repair pathways, leading to the death of the cells.¹⁰³ Especially in BRCA-deficient breast cancer, the repair of DNA damage exclusively depends on the action of PARP1, making the sensitivity of PARP inhibitors higher than others.^{104–106} This scientific evidence provides positive proof of concept for PARP inhibition in BRCA-deficient breast cancers and demonstrates a novel targeted treatment strategy for TNBC.

In 2009, Olaparib, a PARP inhibitor, was clinically validated for its synthetic lethal interaction with BRCA1/BRCA2 deficiency. Further clinical research also evaluated the efficacy, safety, and tolerability of olaparib alone in breast cancer patients and demonstrated that a dosage of 400 mg b.i.d was both safe and effective for patients with BRCA1/2 mutation.¹⁰⁷

In a randomized phase III Olaparib trial of metastatic BRCA mutation breast cancer, 302 HER2-negative metastatic breast cancer patients with a germline BRCA mutation were randomly assigned to either receive olaparib tablets or standard single chemotherapy. The results showed that patients treated with olaparib had a higher response rate and longer median progression-free survival.¹⁰⁸ Based on these clinical trials, the PARP inhibitor olaparib was recently approved for TNBC.

In addition to olaparib, a number of other PARP inhibitors including veliparib, talazoparib, niraparib and rucaparib are currently undergoing clinical trials, with particular focus on their potential use for metastatic breast cancer.^{109–111} One such trial, the I-SPY 2 trial, evaluated the effectiveness of veliparib and carboplatin when added to standard chemotherapy regimens for patients with TNBC. While the addition of veliparib did increase pCR rates from 26% to 52%, its precise impact on patient outcomes remains unclear.¹¹² Another PARP inhibitor that is being evaluated for breast cancer is talazoparib. In the phase III EMBRACA study, talazoparib was compared as a monotherapy against capecitabine or eribulin chemotherapy regimens for patients with BRCA mutation breast cancer. The results of this study showed that median progression-free survival was significantly improved with talazoparib treatment, and interim analysis of overall survival also showed a positive trend. As a result, talazoparib has also received FDA approval for use in the treatment of BRCA mutation breast cancer.¹¹³

There are numerous ongoing clinical trials exploring the potential of PARP inhibitors for early-stage TNBC patients. One such trial is the phase III OlympiA trial, which aims to assess the effectiveness of olaparib treatment for high-risk TNBC patients with germline BRCA1/2 mutations who have undergone standard neoadjuvant chemotherapy and local treatment (NCT02032823). Another phase III clinical trial is currently underway to establish the safety and efficacy of adding olaparib to neoadjuvant platinum-based chemotherapy for TNBC patients (NCT03150576). Beyond olaparib, a Phase I trial is ongoing to evaluate the effectiveness of neoadjuvant veliparib combined with radiation therapy for residual breast cancer following neoadjuvant chemotherapy (NCT01618357).

Anti-Androgen Therapy

Androgen receptor (AR) belongs to the nuclear steroid hormone receptor family, playing a critical role in signaling pathways and regulating gene expression as transcription factors. Emerging evidence indicated that AR signaling is a critical determinant of normal and malignant breast tissue, performing a pivotal function in breast carcinoma progression.^{114,115} In breast cancer, AR is the most widely expressed nuclear hormone receptor, and its expression is always associated with a favorable prognosis. A systematic review examined 7693 patients across 19 different studies, finding that AR is expressed in 60.5% of patients, who exhibited better overall survival (OS) and disease-free survival (DFS) than AR-negative breast cancer patients.¹¹⁶ The LAR subtype of TNBC is enriched in hormonally regulated pathways, predominantly dependent on AR signaling. However, the mechanism of AR in TNBC still ambiguous. Existing evidence suggests that AR is activated in extracellular signal-regulated kinase (ERK) and HER2 signaling through PI3K, Src, and RAS in TNBC.¹¹⁷ Moreover, AR overexpressed cell lines were found to frequently carry PIK3CA-activating mutations. These cells are sensitive to PI3K inhibitors and AR inhibitors, highlighting a correlation between AR and the PI3K pathway.^{118–120}

This evidence leads to new treatment strategies and potential clinical implications for TNBC, and ongoing clinical trials for AR-targeted therapies. The oral nonsteroidal AR antagonist, bicalutamide, has been approved by The US Food and Drug Administration for the treatment of metastatic prostate cancer. Evidence of using bicalutamide's effectiveness in the treating TNBC has been proven in phase II clinical trial where patients with metastatic AR-positive TNBC were given bicalutamide. Among patients with AR-positive tumors, the clinical benefit rate was 19%, and the median progression-free survival was 12 weeks.¹²¹ These findings form the basis of anti-androgen therapy in AR-positive TNBC. Subsequently, another phase II clinical trial with enzalutamide, a more potent AR inhibitor, was conducted. It was reported that 35% of patients showed clinical benefits in advanced-stage AR-positive TNBC.¹²²

Emerging Treatment Strategies

Antibody-Drug Conjugates

In recent years, antibody-drug conjugates (ADCs) have emerged as viable antitumor agents that can deliver cytotoxic payloads on monoclonal antibodies through specific conjugations. ADCs have unique tumor specificity and potency that

traditional drugs cannot match, making them a useful tool in personalized cancer medicine.^{123–125} The clinical use of ADCs is poised to become a significant modality in the therapy of tumors in the near future, with novel ADCs entering clinical studies for the treatment of TNBC patients.

The Human trophoblast cell-surface antigen 2 (Trop-2) has exhibited high potential as a therapeutic target due to its overexpressed in metastatic TNBC.¹²⁶ Sacituzumab-govitecan, an ADC targeting Trop-2, incorporates a humanized monoclonal antibody (hRS7) to deliver the active metabolite of irinotecan SN-38 (govitecan).¹²⁷ The randomized phase III ASCENT (NCT01631552) trial reported a response rate of 33.3% with sacituzumab govitecan, with longer progression-free survival than standard chemotherapy. This led to the approval of the new ADC for refractory metastatic TNBC.¹²⁸

Another novel HER2-targeted ADC, trastuzumab deruxtecan (T-DXd), was designed to deliver topoisomerase I inhibitor to HER2-expressing cancer cells. The phase I study aims to evaluate its antitumor activity and safety in patients with advanced breast cancer expressing low levels of HER2.¹²⁹ The confirmed objective response rate is 37.0%, and the median duration of response of 10.4 months. Moreover, a phase III study compares the efficacy and safety of T-DXd with capecitabine chemotherapy regimen (NCT03734029). T-DXd has demonstrated promising clinical antitumor activity in HER2-negative patients with a manageable safety profile and may provide a novel targeted treatment option for TNBC.

Cancer Stem-Cell Population Inhibitors

It is now evident that certain tumors can be initiated and sustained cancer stem cells, which possess the ability to renew and differentiate themselves to drive tumorigenesis.¹³⁰ Breast cancer stem cells, for example, can repopulate a heterogeneous tumor from a single cell¹³¹ and can be identified through the measurement of aldehyde dehydrogenase activity,^{132,133} assessment of integrin receptors expression, or a decrease in the ability to exclude the ATP-binding cassette (ABC) transporter.¹³⁴ These stem cells exhibit slower rates of proliferation and higher levels of resistance to chemotherapy, which contributes to resistance and accelerated recurrence after traditional chemotherapy therapies.¹³¹ Therefore, exploring the novel target therapies for breast cancer stem cells in combination with chemotherapy may be a potential modality for treating TNBC. Although inhibitors of breast cancer stem cells can be established clearly, the pathways that contribute to the maintenance of breast cancer stem cells, such as the mitogen-activated protein kinase (MAPK), JAK/STAT, Wnt, TGF- β , Hedgehog, and Notch1 pathways, have been identified in independent studies.^{135–139} Apart from that, other agents that target various aspects of CSCs, including specific markers, signaling pathways, dormancy, proliferation, metabolism, autophagy, and drug resistance, have shown promising preclinical results and are now entering clinical trials.¹⁴⁰

MiRNA Targets and Therapies

The dysregulation of miRNAs is known to play significant role in silencing gene expression, suppressing or activating multiple genes in TNBC. This dysregulation can occur through various mechanisms such as amplification, deletion, epigenetic, transcriptional dysregulation or defective miRNA biogenesis.¹⁴¹ These oncogenic miRNAs can act as tumor suppressor genes or oncogenes, ultimately promoting tumor invasion, metastasis, and drug resistance.¹⁴² For instance, miR-155, miR-320a, and miR-205 expression have been linked to lymph node metastasis,¹⁴³ while miR-206 affects the migration and invasion of TNBC cells, and miR-340 inhibits invasion and metastasis by Rho Kinase 1 (ROCK1).^{144,145} Moreover, miRNA-222, miR-5195-3p and miRNA-449 have been found to mediate multi-drug resistance to chemotherapeutic agents via various mechanism in TNBC cells.^{146–148} Beyond this, miRNA regulators also contribute to pathobiology of TNBC by influencing the tumor microenvironment, including inflammation, target expression, and secretion from fibroblasts.¹⁴⁹ For instance, in PTEN-deleted fibroblasts, miR-320 mediates E26 oncogene homolog 2 (ETS2) target to active oncogenic secretome, promoting angiogenesis and invasion in the TNBC microenvironment, thereby enhancing TNBC cell migration and invasion.¹⁵⁰ Additionally, miR-9, a pro-metastatic miRNA, is up-regulated in TNBC tumor cells to transfer to fibroblasts.¹⁵¹ While most of the literature on using miRNAs to target breast cancer is still in the preclinical stage, miRNA therapies are showing great potential for treating TNBC.¹⁵²

Summary and Outlook

TNBC is a unique disease entity characterized by molecular and immunological heterogeneity, which manifests a variety of clinical subtypes. While chemotherapy remains the principal treatment for TNBC, massively parallel sequencing technologies have contributed to our novel understanding of this subtype. These molecular advances have enabled us to exploit promising therapeutic targets for TNBC by targeting actionable genomic alterations and molecular pathways, numerous experimental therapies are ongoing. To update the latest developments. This has resulted in numerous ongoing experimental therapies. To provide the latest developments in TNBC treatment, this article comprehensively reviews the molecular classification of TNBC and targeted therapy developments in signaling pathways, targeted therapy, immunotherapy, PARP inhibitors, antibody-drug conjugates, and androgen receptor blockade. Treatment options for TNBC have evolved from basic cytotoxic chemotherapy to an expanding domain of targeted therapies for this heterogeneous disease. Ongoing efforts of researchers have opened up new avenues of hope for TNBC patients.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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