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TRIPLE-NEGATIVE BREAST CANCER: A REVIEW OF EVOLVING STRATEGIES

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ABSTRACT

Triple-negative breast cancer (TNBC) is a heterogeneous and aggressive group of tumors that are defined by the absence of estrogen and progesterone receptors and lack of ERBB2 (formerly HER2 or HER2/neu) over expression. TNBC accounts for 8%–13% of breast cancers. In addition, it accounts for a higher proportion of breast cancers in younger women compared with those in older women, and it disproportionately affects non-Hispanic Black women. The survival rate for TNBC is generally worse than other breast cancer subtypes. TNBC treatment has made significant advances, but certain limitations remain. Triple negative breast cancer has a negative expression of estrogen receptors (ER), progesterone receptors (PR), and human epidermal growth factor receptors (HER2). The survival rate for TNBC is generally worse than other breast cancer subtypes. Early TNBC outcomes have improved due to the intensification of therapies, including improvements in polychemotherapy and the addition of immunotherapy. Future efforts are needed to identify targetable aberrations for specific drug therapy, prevent immune evasion, and increase social-economic support. The non-availability of specific treatment options for TNBC is usually managed by conventional therapy, which often leads to relapse. The focus of this review is to provide up-to-date information related to pathophysiology, prognosis, treatment, challenges, and future perspectives. The data presented in this paper may be helpful for researchers working in the field to obtain general and information to advance the understanding of TNBC and provide suitable disease management in the future.

Keywords: Triple-negative breast cancer, human epidermal growth factor receptor 2, Small interfering RNA, cytokeratin pairs, tumour immune microenvironment.

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INTRODUCTION

Cancer remains a rising threat in society, with a mortality figure of 8.2 million people documented globally in a given year [1]. Estimates show that by 2030, 13.1 million people will have died from cancer, making it the leading cause of death, aside from cardiovascular disease, worldwide [1,2]. Cancer can occur anywhere in the body and in individuals of all genders [2]. Breast cancer is the most frequently diagnosed malignancy among females and has

surpassed lung cancer, with approximately 2.3 million cases annually [3,4]. This calls for an in-depth understanding of the pathobiology of the disease and the development of more effective therapeutics. Breast cancer is a multifactorial disease involving environmental, hormonal, genetic, and several lifestyle or nutritional factors. Consequently, patients with breast cancer exhibit a variety of clinical, pathological, and molecular peculiarities [5].

The expression profiles of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) categorize the molecular subtypes of breast cancer. Triple-negative breast cancer (TNBC) is ineligible for widely used targeted therapy because it is negative for HER2, estrogen, and progesterone. The usual treatment approach for TNBC is neoadjuvant chemotherapy (NAC) based on anthracyclines (e.g., doxorubicin) and taxanes (e.g., paclitaxel) [6].

However, approximately 50% of patients treated with NAC develop chemo resistance due to chromosomal instability [7]. Unfortunately, clinical results for TNBC are still not up to par, even with advancements in understanding tumor biology. Compared to patients with HR-positive and HER2-enriched disease, whose treatment focuses on particular mRNA expression, siRNA is frequently used to understand gene function and has recently been applied to treat several illnesses. An important milestone in the development of RNA-based medications was reached in November 2019, when the FDA approved the second siRNA-based medication [8].

However, the *in vivo* use of siRNAs is still at a standstill because of their instability, hydrophobicity, and net negative charge [9]. Novel siRNA Drug Delivery Systems (DDS) have rapidly evolved over the last 20 years, including cationic polymer-based [9], exosome-based [10], membrane-camouflaged [11], lipid-based [12] and nanogel-based [13] DDS. Unfortunately, current DDS have specific disadvantages that make *in vivo* application difficult, including large particle size, cytotoxicity, aggregation *in vivo*, and immune response [14]. The median overall survival may surpass five years, and the median overall survival for patients with metastatic disease is approximately 18 months [8].

This highlights the urgent need to develop better treatments for patients must be developed. This review aims to highlight the most pertinent information regarding the underlying molecular profile of TNBC and its possible use in clinical practice. To achieve the combined anti-tumor effects of immunotherapy and chemotherapy, a biomimetic nanogel with tumor microenvironment-responsive properties was created. Two oppositely charged chitosan derivatives and hydroxypropyl- β -cyclodextrin acrylate were used in the formulation of nanogels to precisely control pH responsiveness and entrap the anticancer drug paclitaxel, respectively. The "nanosponge" property of the nanogel-supported erythrocyte membrane allows for the delivery of the immunotherapeutic agent interleukin-2 without compromising its bioactivity. The nanogels significantly improved antitumor activity by inducing calreticulin exposure, improving drug penetration, and boosting antitumor immunity through responsive drug release in the tumor microenvironment. By promoting the infiltration of immune effector cells and reducing immunosuppressive factors, the combination of these medications at low dosages remodels the tumor microenvironment [13]. In this review, we discuss the available treatments for TNBC, their prognosis, drawbacks, difficulties, and potential future paths.

Background

This disease is considered a group of biologically different diseases rather than a single clinical syndrome. Evidence from molecular profiling techniques has established that gene expression variability is a key factor in the prognosis of breast cancer. The use of estrogen receptors, progesterone

receptors, and human epidermal growth factor receptors has dramatically changed treatment strategies, as targeted therapy is applied to different types of breast cancer. However, improvements in the treatment of receptor-negative breast cancer are still lacking [15,16].

Currently, chemotherapy is the most effective treatment for TNBC, as there are no known molecular targets available for treatment. The most commonly used regimens for TNBC are based on either anthracycline or taxane, which may shrink tumors before or after surgery [17]. However, in the majority of TNBC patients, tumors develop both intrinsic and acquired mechanisms of resistance, inhibiting the effectiveness of therapy. Resistance is caused by multiple pharmaceutical mechanisms, including genomic instability, changes in cell cycle regulation, dysregulation of programmed cell death (apoptosis), and adaptive processes within the tumor microenvironment [18,19].

Recently, gene silencing has received increasing attention as a possible alternative therapy for TNBC. Small interfering RNA (siRNAs) can selectively down regulate oncogenes and other pathways related to the development of resistance by targeting complementary mRNA sequences. There have been clinical advances in the use of RNA-based drugs, and the regulatory approval of siRNA drugs for non-oncological indications has stimulated further interest in developing RNA-based drugs for the treatment of cancer [20]. However, siRNA therapies also face several major obstacles related to their delivery, such as rapid breakdown by enzymes, poor uptake by cells, rapid elimination from circulation, and inadequate accumulation in tumors [21].

In addition, researchers have obtained positive results with nanocarriers that contain biological materials, such as membranes made from cells, to improve the time that the nanocarrier remains in circulation, decrease the chance that the nanocarrier will be identified and removed from the body by the immune system, and increase the targetability of the nanocarrier towards the tumor. These systems can also facilitate immunogenic cell death, enhance the immune response by promoting the migration of immune effector cells into the tumor, and modulate components of the tumor microenvironment that inhibit the immune response. Taken together, these data suggest that novel nanotechnology-based systems may provide opportunities to circumvent the limitations of current TNBC treatment [22].

PATHOPHYSIOLOGY

Triple-negative breast cancer (TNBC) is defined as breast cancer without the presence of the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) [22]. Biologically, TNBC lacks these receptors compared with other types of breast cancers, which is an important factor in its aggressive behavior, and there is

only limited treatment options designed to target TNBC specifically [23].

At the genomic level, TNBC is characterized by high levels of chromosomal and genetic instability, extensive copy number alterations, and a very high mutational load [24]. The most frequently mutated gene in TNBC is TP53, which has a mutant allele in over 80% of patients with TNBC, leading to impaired DNA repair, defective cell cycle regulation, and increased heterogeneity in the multiple cancer cells of a single patient with TNBC [24,25].

In turn, these genetic alterations enable the rapid evolution of cancerous cells and contribute to an early rate of progression of the disease. High levels of basal cytokeratin pairs (that is, CK5; CK6; CK14; CK17) along with epidermal growth factor receptor activation are indicative of a specific molecular phenotype for triple negative breast cancers (TNBC). This phenotype is characterized by a high rate of proliferation, poor levels of differentiation, and increased levels of invasion. Epithelial-mesenchymal transition (EMT) pathways further promote increased plasticity within cells and promote cell migration and/or metastasis. [26,27].

Many different dysregulated oncogenic signaling pathways are present in TNBC, leading to tumor progression. The PI3K/AKT/mTOR pathway is often aberrantly activated due to inactivation or loss of function of the tumor-suppressor gene PTEN (Phosphatase and tensin homolog), leading to continued survival and resistance to apoptosis. Other pathways, including MAPK (Mitogen-Activated Protein Kinase) or Wnt/ β -catenin signaling contribute to prolonged proliferation and metabolic adaptations [19,28].

The tumor microenvironment (TME) is the main contributor to the pathophysiology of TNBC. TNBC is associated with hypoxia, reduced extracellular pH, and substantial stromal remodeling, which leads to aggressive tumor characteristics and immune escape. Tumor-infiltrating lymphocytes in TNBC are typically associated with other immune features, including immune suppression, immune activation, and tumor-associated macrophages, which hinder immune responses against tumors [29,30].

Another characteristic feature of TNBC is the enrichment of cancer stem-like cells, which are capable of self-renewal and contribute to the initiation of tumors, heterogeneity, recurrence, and resistance to therapy [31]. These cancer stem-like cells exhibit robust survival abilities and actively interact with the microenvironment, contributing to regeneration in response to cytotoxic stress [31]. In aggregate, the pathophysiology of TNBC includes genomic instability, aberrant signal transduction pathways, cell invasiveness, and tumorigenic microenvironments, thereby making it more aggressive and with a poor prognosis in comparison to other breast cancer varieties [23,27].

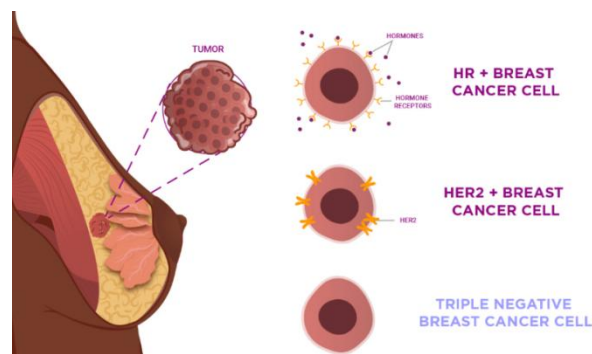


Figure 1: Triple-negative breast cancer cell

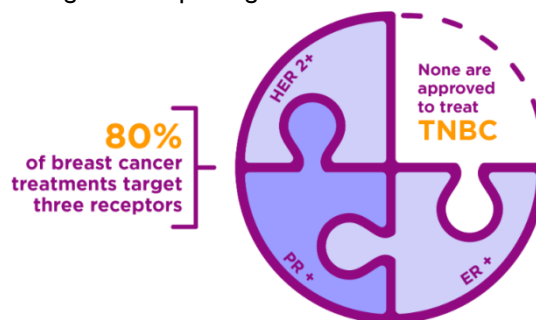


Figure 2: TNBC targeted receptors

PROGNOSIS

Triple-negative breast cancer has an overall poorer prognosis than hormone receptor–positive and HER2-enriched breast cancer subtypes because of its aggressive biological behavior, and there are no approved targeted therapies available [19,23,24]. Clinically, patients with TNBC tend to be younger than those with the other two subtypes of breast cancer and have higher-grade histological tumors and increased tumor proliferation indices. These features contribute to an accelerated pace of disease development and poor clinical outcomes relative to patients with other forms of breast cancer [19].

Patients with TNBC appear to respond positively to standard chemotherapy in the early phases of the disease; however, they also have a high rate of relapse (i.e., recurrence of the disease) within three to five years of diagnosis. [19,24]. Patients with TNBC have an increased risk of developing distant metastases, particularly in the visceral organs (e.g., lung and brain), compared with metastases to the bone. Bone metastasis occurs more frequently in patients with other types of breast cancer that express hormone receptors. [19,24].

These recurrence patterns have a significant impact on patient outcomes (i.e., such as overall survival and disease-free survival). Genomic instability and intratumoral heterogeneity are two major determinants of the prognosis of triple-negative breast cancer (TNBC) at the molecular level [25,26]. As demonstrated by extensive genomic studies, TNBC is characterized by frequent alterations in DNA repair mechanisms, tumor suppressor genes, and cancer-promoting signaling pathways, which allow rapid clonal evolution and the development of resistance to

therapy [25,26]. Similarly, single-cell sequencing analyses have shown that chemotherapy can provide a mechanism for the selection of resistant populations of tumor cells, leading to relapse and/or decreased long-term survival [6].

An emerging understanding of the distinct molecular subtypes of TNBC may provide insight into the variability of prognosis among patients diagnosed with TNBC [27]. Some subtypes of TNBC (e.g., basal-like and mesenchymal-like) exhibit more aggressive behavior due to enhanced invasive capabilities and the ability to develop resistance to standard-of-care therapy [27]. Thus, the heterogeneity observed in TNBC makes it difficult to accurately predict prognosis and further emphasizes the need for subtype-specific treatment paradigms. Among patients with metastatic disease, prognosis is particularly poor, with median overall survival durations of 12–18 months, which is significantly less than that of patients with other breast cancer subtypes [8,19,24].

There have been several recent advances in immunotherapeutics as well as in the development of novel drug delivery systems; however, long-term clinical benefits from these therapies remain limited to only a subset of patients, indicating that further research is needed to improve the prognostic markers and treatment options available for these patients [8,29].

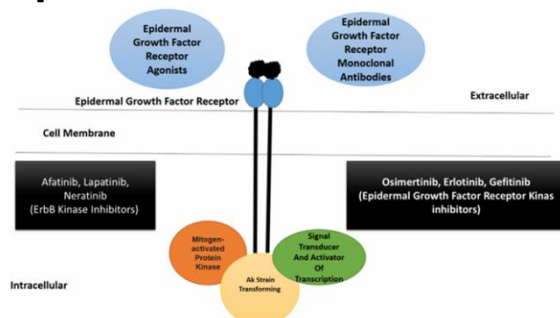


Figure 3: A schematic illustration of epidermal growth factor receptor signaling pathway along with activators and inhibitors

TREATMENT

Monotherapy approaches

In the context of monotherapy, the most commonly used therapeutic regimens include the use of cytotoxins, most notably chemotherapy, due to the lack of expression of the estrogen receptor, progesterone receptor, and HER2. Consequently, other forms of hormone therapy or HER2-targeting therapy cannot be used as prospective therapies for TNBC [23,24]. Notably, the most used chemotherapy agents that have been recognized as standard treatment regimens include anthracyclines, most notably doxorubicin, taxanes, most notably paclitaxel, and platinum agents, which have all demonstrated the ability to trigger DNA-DNA cross-links and cell division arrest in tumor cells as the form of action

used for the development of their antitumor response [19,24].

Although in the initial evaluation of patients treated with the aforementioned formulation, tumor reduction has been noted to be significant, several reports have noted that chemoresistance can develop using monotherapy, with patients having relapsed diseases and limited survival outcomes [6,26]. As a result, the regimen has been used for patients who have fallen into the category requiring treatment in either outpatient settings or patients who cannot tolerate the combination regimen [8].

Multidrug

The mainstay of therapy for TNBC is multi-drug chemotherapy, especially in neoadjuvant and adjuvant settings [19,23]. The standard chemotherapy regimen generally consists of anthracyclines and taxanes, which target tumor cells differently, thus improving their antitumor effects [24]. Platinum-based agents, such as cisplatin and carboplatin, are also commonly used to treat TNBC because of its defective mechanisms for DNA damage repair, and these agents can act by DNA cross-linking [25,26].

However, despite the high pathological complete response in tumors treated with multi-drug therapy, relapse continues to be a problem in the early stages of treatment [6,19]. Single-cell and genomic studies have shown that chemotherapy induces selective pressure, thereby promoting clonal evolution in tumors, which adversely affects prognosis [6,26]. This highlights the limitations of treatment with traditional cytotoxic agents.

Combination therapy (Chemotherapy, Targeted Therapy, and Immunotherapy)

Combination therapy has been identified as a potential solution for overcoming resistance in patients with TNBC [8,24]. Notably, the combination of chemotherapy with immunotherapy holds promise in the management of TNBC because of the ability of this malignancy to have more immune cell infiltrations than other forms of breast cancer [29].

Immunogenic cell death induced by chemotherapy increases tumor antigenicity, thereby sensitizing it to immunotherapy. Targeted therapies are also being tested for combination therapies, including antibody-drug conjugates, which selectively deliver cytotoxic agents to tumor cells with minimal systemic toxicity [1]. These agents have the potential to enhance the specificity of treatment with minimal adverse effects of chemotherapy [1,8]. In addition, therapeutic combinations have been proven to alter the tumor environment by promoting the infiltration of effector cells into tumors with reduced immunosuppressive signals [29].

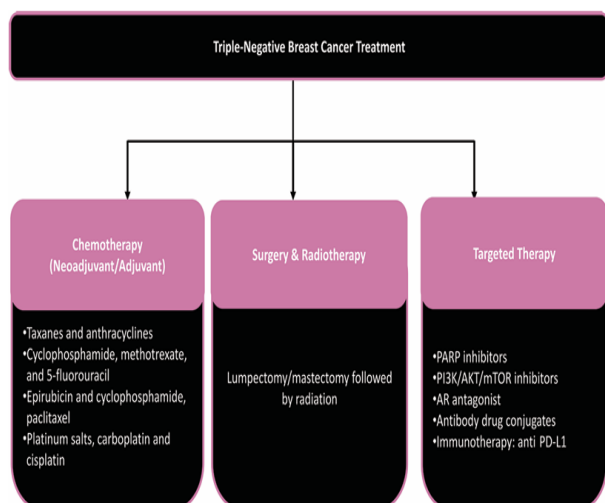


Figure 4: Options for treatment of TNBCs (AR = androgen receptor, PARP = poly (ADP-ribose), PI3K/AKT/mTOR = phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin).

ADVANCED AND EMERGING TREATMENT STRATEGIES

Recent improvements in nanotechnology and nucleic acid therapy have encouraged the development of new and innovative strategies for the treatment of TNBC [20,21]. The potential of siRNA-based strategies has been confirmed; however, clinical applications face challenges such as delivery, stability, and immune responses [14,21]. To address these challenges, various delivery methods have been explored and developed, including lipid vehicles, exosomes, membrane-activated vesicles, and nanogels [10,12-14]. For example, tumor microenvironment-responsive nanogels, which can deliver chemotherapeutic and immunotherapeutic agents concurrently, have been shown to have enhanced antitumor activity by enhancing penetration, inducing immunogenic cell death, and stimulating antitumor immunity [13,22]. These combinatorial approaches with nanotherapy hold promise as a potential avenue for TNBC treatment, particularly for overcoming treatment resistance and improving survival [8,20].

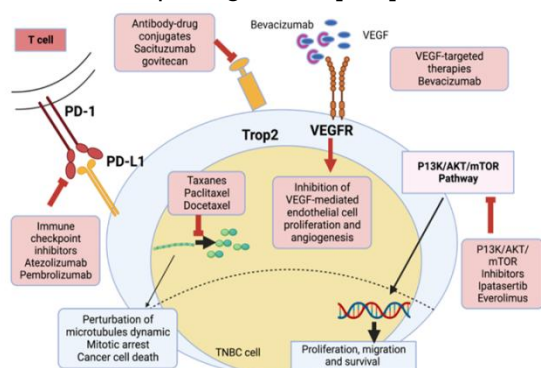


Figure 5: Various triple negative breast cancer treatments available in the clinic. As far as therapeutic strategies are concerned, several approaches have been proposed for both patients with early and

advanced triple negative breast cancer. These include immunotherapy, deoxyribonucleic acid (DNA)-interfering agents, and targeted therapies.

CHALLENGES

One of the major challenges in the treatment and management of triple-negative breast cancer is the inherent molecular and clinical heterogeneity seen in the disease, which significantly affects patient responses to treatment [24,27]. Genomic and transcriptomic analyses have shown that TNBC comprises several molecular subtypes, which are associated with different oncogenic pathways leading to the development of the disease, which makes it difficult to find effective targets for therapy [25,27]. Another major challenge associated with TNBC tumours is the quick development of therapeutic resistance. TNBC usually presents an effective response to chemotherapy, but tumour relapse usually arises following the development of therapeutic resistance, particularly because TNBC tumours usually possess genetic instability, which leads to tumour evolution and pressure, thereby developing resistance [6, 26].

Recent findings using single-cell sequencing technologies have shown that tumour relapse arises because chemotherapy fosters the outgrowth of resistant tumour cells, leading to poor long-term patient survival [6]. The absence of well-established targeted therapies also remains a critical limitation. Unlike hormone receptor-positive or HER2-positive breast cancers, TNBC lacks validated molecular targets, which restricts treatment options primarily to chemotherapy [23,24]. To date, antibody-drug conjugates and emerging targeted agents demonstrate clinical benefit in very selected patient subsets only [1, 8].

Besides this, the tumour immune microenvironment is also a significant obstacle to effective therapy. TNBC, being considered relatively immunogenic, nonetheless has potential limitations to therapies due to the presence of immunosuppressive cells and signalling pathways. Variability in immune infiltration and immune checkpoint expression is yet another factor that complicates patient selection and therapeutic response [29].

Finally, the translation of advanced therapeutic platforms, like siRNA-based therapies and nanomedicine, is highly challenging. Each modality faces many challenges regarding in vivo stability, delivery efficiency, immune activation, and off-target effects, which hinder its extensive clinical application [14,21]. Most of the delivery systems developed so far show toxicity, aggregation, or poor tumour specificity that compromise their therapeutic efficacy [10-14].

FUTURE PERSPECTIVES

Advancements in treating TNBC will depend on improved molecular characterisation and precision medicine. Molecular and transcriptional

characterisation may inform subtype classifications, allowing for identification of possible targets and creating targeted strategies to deliver individualised therapies [25,27], resulting in improved patient selection and better therapy response. Combination therapy could be an exciting way to combat resistance and drive better results than single-agent therapies. Combining chemotherapy with immunotherapy or targeted agents has the potential to increase the efficacy of antitumor therapy; this is accomplished by attacking both the malignant cell itself and the surrounding environment [8,22,29]. A strategy to induce immunogenic cell death would enhance immune recognition of the tumour and provide opportunities for greater responses for patients receiving immunotherapy [22].

Future management of triple-negative breast cancer is also highly dependent on being able to effectively deliver specific drugs to target cells within the tumour. Advances in drug delivery systems, especially those based on nanotechnology, including exosomes and responsive nanogels, provide an opportunity to enhance the pharmacokinetics of anticancer agents by increasing their stability and ability to penetrate the tumor as well as providing controlled release of these agents from the delivery system [10-13]. The synergistic effect of using both chemotherapy and immunotherapy together at the same time through these new delivery systems may be able to produce enhanced antitumor activity while reducing systemic toxicity [13].

The ongoing development of nucleic acid-based therapeutics (including siRNA-based therapies) also provides a unique opportunity to effectively target oncogenic drivers that have previously been considered "undruggable" [20,21]; however, continued optimisation of drug delivery technologies to these nucleic acid therapies and the mitigation of immune-related side effects will be critical to bringing these therapies to the clinic [14,21].

Finally, successful solutions to the existing problems of tumour heterogeneity, therapeutic resistance, and drug delivery route will lead to improved patient outcomes through the realisation of integrated, multimodality treatment strategies in future TNBC therapy [8,24,29].

CONCLUSION

TNBC is merely an operational term that stemmed from the fact that, in the mid-2000s, the only systemic therapy available for patients with ER-, PR-, and HER2-negative disease was chemotherapy. This term has been shown to encompass a collection of distinct diseases, which only happen to share the lack of ER, PR, and HER2 as a common denominator but are vastly different in terms of their histologic features, genomic characteristics, clinical behavior, and response to therapy. The key to developing targeted therapies for TNBC will depend on understanding the molecular mechanism for the development of these cancers. Recently, TNBC has received a lot of attention. There

have been numerous attempts to improve treatment for this form of breast cancer, which stands as the most aggressive. TNBCs currently treated with chemotherapy, surgery, and radiotherapy, with chemotherapy being the most common method.

In conclusion, TNBC is a difficult and complex disease entity that is both confusing and frustrating for researchers, physicians, and patients. To date there are multiple approaches attempting to improve care of triple negative breast cancer patients, including DNA damaging agents like platinum's, targeted Epidermal Growth Factor Receptor(EGFR), and Vascular Endothelial Growth Factor(VEGF) inhibitors, and, poly [ADP-ribose] polymerase (PARP) inhibitors; however, none have been as clinically successful as anticipated and more targeted therapies need to be developed and explored. Among all breast cancers, TNBC has the worst prognosis, in addition to suppressed immunity of the patient. Hence, understanding the TNBC molecular signaling pathway in the tumor microenvironment by applying multidisciplinary research will greatly advance TNBC diagnosis and therapy. Numerous clinical trials on TNBC therapy are underway. In addition, imaging, and pathologic biomarkers to predict tumor recurrence and response to chemotherapy are under investigation. The use of these biomarkers may pave the way to personalized treatment for patients with TNBC.

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DISCLOSURES OF CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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