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Personalized Approach in the Treatment of Triple Negative Breast Cancer: Literature Review and Perspectives

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Abstract

Triple Negative Breast Cancer (TNBC) refers to a tumor lacking estrogen and progesterone receptors expression and is classified as HER2 negative, while the proliferative activity index (Ki67) shows high values. Thus, TNBC is characterized by the lack of "standard receptors." Recent studies have shown the need for a more detailed classification related to TNBC due to a high variability within the subtypes. Limited therapy choices, aggressive form, and early recurrence are all current concerns. The search for new targeted drugs and points application are highly important in the development of therapy for TNBC.

Keywords: Breast cancer; Triple negative subtype of tumor; Inherited mutations; Androgen receptors

Abbreviations

BC: Breast Cancer; TNBC: Triple Negative Breast Cancer; Ki67: Proliferative Activity Index; IHC: Immunohistochemistry; ER: Estrogen Receptor; PR: Progesterone Receptor; HER2: Human Epidermal Growth Factor Receptor-2; BRCA 1.2: Breast Cancer Genes 1.2; mTNBC: Metastatic Breast Cancer; AR: Androgen Receptor; BL1: Basal-Like 1; BL2: Basal-Like 2; M: Mesenchymal subtype; MSL: Mesenchymal Stem-Like subtype; IM: Immunomodulatory subtype; LAR: Luminal Androgen Receptor subtype; BLIS: Basal-Like Immunosuppressive; BLIA: Basal-Like Immune-Activated; PD-L1: Programmed Death-Ligand 1; VEGF: Vascular Endothelial Growth Factor; DNA: Deoxyribonucleic Acid; NACT: Neoadjuvant Chemotherapy; NPCT: Neoadjuvant Polychemotherapy; pCR: Pathomorphological with Complete Response; mRNA: Mitochondrial Ribonucleic Acid; Trop-2: Trophoblastic Cell Surface Antigen 2; PI3K: Phosphoinositide 3-Kinases; HR: Hazard Ratio; CI: Confidence Interval; OR: Odds Ratio; PFS: Progression-Free Survival; EMT: Epithelial-Mesenchymal Transition

Materials and Methods

50 sources were selected from the databases of PubMed, Scopus, eLibrary from 2020 to 2023 and analyzed for current trends in the treatment of TNBC.

Goals and Objectives

Highlight the changes and approaches in the diagnosis and therapy of triplet negative cancer depending on the subtypes.

Introduction

Breast cancer is a heterogeneous disease requiring different approaches in diagnosis and treatment. Triplet negative cancer, is one of the subtypes of breast cancer and the most malignant, recurrence, it mainly affects young women under 40 years. A closer examination of the molecular forms shows in this group of patients several variants. Molecular genetic studies have allowed to reveal of the disease course, estimate prognosis, and also to determine the targets of influence on various cell targets. TNBC now tends to be the most studied subtype, and new drug discoveries offer

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hope for a better treatment and outcomes.

Analysis of Literary Sources

Epidemiology

Breast cancer is the most common cancer in women. At the end of 2021, 4,023,446 patients with malignant neoplasms were under surveillance in Russia. The majority of patients present malignant neoplasms of the breast, and account for 19.1% (767,881) [1]. There are 526.4 cases of breast cancer out of 100,000 people. For stages I-II, the diagnosis is established in 73.7%, for stage III in 18.0%, in advanced stage IV in 25.9%.

According to the latest GLOBOCAN study from 2020, this is the most common cancer in women, accounting for 2,262,419, or 24.5% of all cancers worldwide [2].

Diagnosis

Currently, the diagnosis of TNBC has been by imaging and immunohistochemical testing. Imaging techniques mainly include mammography, ultrasonography of breasts, and Magnetic Resonance Imaging (MRI). Mammography allows early visualization of the tumor providing the tumor's localization, size, and structure. Ultrasonography is widely used for small tumors that cannot be seen on mammography. For the classification of focal lesions, BIRADS is used. In addition, the use of MRI improves the rate of detection of tumors [3]. Invasive screening methods include sentinel node biopsy with the use of radionuclide testing, and fluid biopsy evaluating biomarkers in the blood play key role in the diagnosis.

The molecular classification of breast cancer includes five major subtypes. Immunohistochemistry (IHC) is commonly used in the detection of these subtypes and detects the expression of receptors on the surface of tumor cells - Estrogen Receptors (ER), Progesterone Receptors (PR) and oncoprotein HER2/neu.

Based on that, BC is divided into the following types: Luminal A, Luminal B (HER2+), Luminal B (HER2-), non-Luminal (HER2+), Triple Negative (Table 1). These subtypes have different prognosis, survival rates, and management strategies.

Characteristics of BC subtypes

According to many studies and literatures, Triplet Negative Breast Cancer occupies a special place in the structure of BC. TNBC is a highly heterogeneous cancer, aggressive, high risk of recurrence and metastases than other subtypes of breast cancer.

In 2019, according to Fayaz et al. TNBC account for 12% of BC. The first stage is identified in 15%, the second stage in 43%, the third stage in 35%, and the fourth stage in 7%. Subclavian lymph nodes involvements were found in 82% of patients. The 10-year survival rate for patients with TNBC was 66% overall (with clear dependence on stage 1: 92% for stage 1, 80% for stage 2, 49% for stage 3, 0 for stage 4), 59% for disease-free, 72% for those without metastases, and 77% for those without local recurrence [4].

Pathologic classification of TNBC is defined as an absence of estrogen and progesterone receptors (0% IHC) and negative HER2 (0-1+ IHC or no HER2/neu FISH amplification <2.0) [5].

TNBC is a low-grade tumor with a high mitotic index and high metastatic risk. These characteristics of TNBC contribute to its aggressive course and the lack of receptors for therapeutic actions. Histologically, TNBC is ductal adenocarcinoma.

Table 1: 2023 Clinical Guidelines, RUSSCO.

Luminal A	Luminal B-	Luminal B+	HER2 +	TNBC
ER +	ER +	ER +	ER-	ER -
HER2 -	HER2 -	HER2 +	HER2 +	HER2 -
PR >20%	PR< 20%	PR any	PR -	PR -
Ki-67< 20%	Ki-67 >30 %	Ki-67 any	Ki-67	Ki-67 >30%

Sources report that 10% to 15% of contralateral breast cancers occur, as well as metachronous neoplasms 8 to 15 years after the primary tumor is diagnosed. These tumors metastasize to the lungs and the brain in 40% of cases, to the liver and bone in 15% [6].

Due to its specific phenotype, TNBC less responds to endocrine therapy or molecular-targeted therapy. Treatment options for TNBC are often: Cytotoxic chemotherapy, surgery, and radiation therapy. However, the treatments reveal some disadvantages including: Incomplete surgical Resection (R1), inappropriate toxicity, low local drug concentrations in the disease site, and limited drug penetration due to abnormal vasculature. Moreover, traditional method of drug kinetics evaluation includes drug concentrations in plasma, which is not a reliable method for chemotherapeutic pharmacokinetics evaluation.

Thoracoscopy is an area of research that uses a combination of diagnostic and therapeutic agents in a single dosage form to target the pathological site by providing real-time monitoring of the drug. Thoracoscopy is a precious tool in personalized medicine because it can be used simultaneously for the detection, treatment and management of cancer diseases.

Nanomedicine allows the targeted delivery and controlled release of drugs in the tumor site, thus altering the bioavailability and pharmacokinetics of the drugs while increasing permeability and retention in the tumor and minimizing serious side effects in healthy cells [7].

Heterogeneity of TNBC, understanding the molecular biology of specific tumor subtypes will help personalize treatment, and also to reduce the risk of severe side effects of therapy.

In 2014, Lehmann et al. analyzed expression profiles of 2,188 genes in 587 patients and identified 6 different tumor subtypes that differ in biological properties: Basal-Like 1, 2 (BL1, BL2); Mesenchymal (M), Mesenchymal-Stem Like (MSL), Immunomodulatory (IM), Luminal Androgen Receptor (LAR). The remaining variants were classified as Unstable (UNS). In addition, the authors divided the cell lines of TNBC according to this classification.

BL is the most common molecular subtype (BL1 22%, BL2 12%).

BL1 is characterized by impaired expression of genes that regulate cell cycle and DNA repair: MYC amplification, PIK3CA, CDK6, KRAS, FGFR1, IGF1R, CCNE1, CDKN2A/B; BRCA2, PTEN, MDM2, RB1, TP53 deletions.

BL2 is associated with (EGFR: Epidermal Growth Factor Receptor, NGF: Nerve Growth Factor, Wnt/b-catenin) [8].

The BL subgroup is extremely aggressive and proliferative, with cancers of subtype BL1 expressing genes that control the cell cycle, and tumors of subtype BL2 expressing growth factor pathways. Both types are known to produce a high level of abnormal response to neoadjuvant chemotherapy. The mutation rate of TP53 (80%) is also high. Protein loss is RB1 (Retinoblastoma) and BRCA1. Activation

of the PI3K (either *via PIK3CA* gene mutations (about 9%) or loss of negative INPP4B and/or PTEN regulators) improved proliferation index with hyperactive FOXM1 as a transcription index.

Genetic similarity between basal-like BC and serous ovarian cancer is noted. This similarity included high ATM and TP53 mutation rates, high AKT3 and MYC expression levels, inactivation of BRCA1 and BRCA2, loss of RB1 protein, and cyclin E1 amplification. About 20% of basal-like cancers are associated with a BRCA mutation that may be sensitive to platinum and/or PARP inhibitors. Amplification included PIK3CA (49%), KRAS (32%), BRAF (30%) and EGFR (23%). Another, less common amplification has been seen in FGFR1, FGFR2, IGFR1, KIT, MET, and PDGFRA. Deletions have been observed in PTEN and INPP4B, which cause PI3K pathway activation [9].

About 75% of TNBC express basal markers, so the triple negative subtype is usually mistaken entirely for the basal subtype, but these concepts are not entirely synonymous [10].

The IM subtype (18%) is characterized by overexpression of genes associated with the realization of the immune response: Metabolic pathways of Natural Killer (NK), helper T (Th), B cells, Dendritic (DC) cells, as well as IL-7 and IL-12 related signaling pathways, as well as signals *via* the main pathways of immune signaling (NFKB, TNF and JAK/STAT signaling). The IM subtype in terms of biological properties in most cases corresponds to medullary carcinoma.

The MSL subtype (10%) is associated with low expression of proliferation-regulating genes and high expression of stem cell-associated genes (ABCA8, PROCR, ENG, ALDHA1, PER1, ABCB1, BCL2, BMP2). Additionally, cells often express stem cell markers (BMP2, ENG, KDR., NGFR, NTSE, PDGFR, VCAM1).

Sub-type M (21%) is characterized by disorganization of signaling pathways regulating cellular migration, receptor-extracellular matrix interactions, and differentiation (Wnt/b-catenin, TGF-b; transforming growth factor beta).

M and MSL subtypes have similar gene expression profiles, including TGF-β, mTOR, Rac1/Rho, Wnt/β-catenin, FGFR, PDGFR, and VEGF signaling pathways. These signaling pathways play an important role in EMF processes and the properties of CD44+ CD24 stem cells - a population of normal breast cells.

The LAR subtype (9%) differs substantially from other tumor variants in that it produces high levels of androgen receptor expression (10 times higher than other types) and overexpression of genes associated with steroid hormone biosynthesis.

Gene expression in the LAR group was the most differentiated among the TNBC subtypes. This subtype is ER-negative but is also enriched by hormonally regulated pathways including steroid synthesis, porphyrin metabolism, and androgen metabolism [8,11].

More recent studies have demonstrated that the immunomodulatory and mesenchymal stem-like subtypes do not correlate with independent subtypes, but instead reflect background expression by the presence of infiltrating lymphocytes and tumor-associated mesenchymal cells. Tumor-Infiltrating Lymphocytes (TILS), both Intracranial TIL (ITIL) and Stromal TIL (STIL), play a predictive role in the treatment of early TNBC and have been evaluated in these settings as immunotherapy response biomarkers.

According to this finding, the classification of TNBC Lehmann has been revised to four subtypes: Basal-Like type 1 (Basal Like 1-BL1), basal-like type 2 (Basal Like 2-BL2), mesenchymal (Mesenchymal-M), and luminal androgen receptor (luminal androgen receptor subtype-LAR subtype) [12].

In 2015, Burstein et al. conducted a study aimed at modifying the criteria and refining the number of molecular subtypes of TNBC in accordance with expression profiles of 80 genes. The analysis identified four molecular subgroups, determined by the overexpression or amplification of a number of genes, and identified specific biomarkers for each. They are named as:

1) Luminal Androgen Receptor (LAR): Androgen receptors, Mucin (MUC 1);

2) Mesenchymal (MES): IGF-1, ADRB2, EDBRB, PTGER 3/4, PTGFR, PTGFRA;

3) Basal-Like Immunosuppressed (BLIS): VTCN1;

4) Basal-Like Immune-Activated (BLIA): CTLA-4. The subgroups proved to be predictive for the relapse-free (p=0.019) and tumor-specific survival (p=0.07). In both cases, the prognosis is worse and classified as: BLIS>MES>LAR>BLIA [13].

Let's have a closer look at on each of them.

Basal-like subtype

Basal-like type 1 (basal-like 1 subtype), or immune-activated type (immune-activated), is characterized by high Ki-67, high rates of DNA damage and cell cycle-regulating genes, particularly TP53 mutations, high MYC, CDK6, or CCNE1 amplification, and deletion/disappearance of mutations in BRCA2, PTEN, MDM2 [14-16].

Basal-like type 2 (basal-like 2 subtype), or immunosuppressive (immunosuppressed), is associated with increased metabolic pathway activity and growth signal factors. These tumors have a high proliferative phenotype, and there is a decrease in B and T cells and NK cells in both the cytokine and immune pathways, which ultimately determines the worst prognosis [17,18]. Almost all cell lines with BRCA1 and BRCA2 mutations have gene expression patterns that correlate with the basal-like subtype, proving the current perception that BRCA mutation carriers have a distinctive basal-like phenotype [19].

Tumor Stem Cells (TSC) of the BC were isolated in 2003 by Al-Hajjtal. Scientists have identified high expression of Epithelial Specific Antigen (ESA+) and CD44 marker ($CD44^+$) on the TSC surface, as well as absence or low expression of CD24 ($CD24^{-/low}$). According to studies, a large number of stem cells found in the biopsy of primary tumor before the start of drug therapy is a predictor of poor prognosis. Elevated levels of TSC have been found in basal-like tumors.

Consequently, quantitative TSC analysis can be used to guide treatment, decisions and prognosis. After determination of CD44 and CD24 markers in BC tumor samples, a correlation was found between high primary tumor marker content and the presence of distant metastasis of BC [20].

Immunophenotypic assay results of TSC in biopsy material of TSIT prior to treatment showed that cells with phenotype $CD44^+/CD24^{-/low}$ were detected in the biopsy specimens of all the patients examined. In 48% of tumors (31/65), the cell share was ≤ 10%; in 46% of tumors (30/65), the share was 10% to 50%; and in 4 cases, it was >50%. The median share of TSC is 10.9%. For a mutation in the BRCA1 gene, the proportion of $CD44^+/CD24^{-/low}$ cells was 5.0; 6.3; 9.7;

30.0; and 42.5%. After identification of CD44 and CD24 markers in BC tumor specimens, a correlation was found between high primary tumor marker levels and the presence of distant metastases of BC. These studies use a quantitative TSC analysis after various types of chemoradiation treatment in patients with TNBC.

It has been suggested that TSCs play a big role in the formation of tumor chemoradiation resistance, as they have low proliferative activity, high expression of ATP-binding cassette transporters. The persistence of the TSC subpopulation after chemotherapy may be associated with the transformation of some cells to the TSC pool. $CD44^{+}/CD24^{-/low}$ phenotypes were found to be most common in basal-like BC and BRCA1-associated tumors [6].

Mesenchymal: This subtype of triple negative cancer demonstrates an expression profile that reflects the presence of mechanisms that ensure the processes of cellular differentiation and movement, including the processes underlying the epithelial-mesenchymal junction. The features of the mesenchymal variant include low expression of claudin, the presence of components interacting with the receptors of EGF and G-protein, as well as the predominance of genes associated with the phenomena of angiogenesis and Cellular Stem Cells (CSC) [21,22]. It has a high expression of PD-L1. Has marked metastatic tumor potential with predominant hematogenous dissemination to lung tissue [23].

LAR subtype (luminal androgen receptor subtype)

Androgen receptors are type 1 nuclear receptors, and are members of the steroid receptor family. When inactivated, they are complexed with heat shock proteins and localized to the cytoplasm. There are two ways in which receptors can be activated: Ligand-dependent and ligand-independent. Ligand for these receptors are androgens. The ligand-dependent pathway of receptor activation consists in binding to androgens and moving the ligand-receptor complex to the nucleus, where it is then recognized by ligand-dependent regions of the genome and provides for the implementation of the hormone action. The ligand-independent pathway of AP activation is *via* the PI3K/Akt, ERK, mTOR, Wnt/β-catenin signaling pathways, and *via* binding to specific proteins such as FOXA1 [24]. The LAR subtype represents- 10% to 15% of TNBC. The LAR subtype is characterized by a high expression of Androgen Receptors (AR), low Ki-67 index values [25]. Therefore, this type of tumor has the highest resistance to neoadjuvant chemotherapy using anthracyclines and/or taxanes, with a complete tumor response rate of just over 14% [26].

LAR tumors, in contrast to basal phenotype breast carcinomas, have extremely proliferative activity and are characterized by cellular immobility. The LAR subtype of triple negative BC is associated with older age, with histologic apocrine differentiation and low Ki-67 values [12].

Preclinical evidence suggests that the effect of Androgen Receptors (ARs) depends on the tumor subtype: In cancer cells that are positive for estrogen receptors, Activity (ARs) can inhibit tumor growth. In TNBC (AR), an oncogenic effect appears to persist. Regarding the prognostic role of expression (AR) in patient groups, available evidence supports an association between expression (AR) and a favorable prognosis for estrogen receptor-positive tumors. For TNBC, some studies have shown a favorable prognosis with expression (AR), some show no results, and others show a relationship between expression (AR) and poor outcome. Different assessment and evaluation methods (AR), heterogeneous patient cohorts, and a short follow-up period may have produced these conflicting results [27].

Studies have shown that *in vivo* developing from specific LAR-cell lines of tumors exhibit extremely high sensitivity to the antiandrogenic nonsteroidal drug bicalutamide [11,28].

In contrast to the basal-like and mesenchymal subtypes of triple negative BC, some literature shows that LAR cell lines have nearly the same sensitivity to CDK4/6 inhibitors as the RE-positive MCF7 cell line [29,30].

In 2016, Liu et al. conducted integrated transcriptional analysis of messenger (mRNA) and Long noncoding RNA (IncRNA) and proposed a classification based on abnormalities in key processes of carcinogenesis.

Immunomodulating subtype (IM, cluster A) is associated with immunogenesis: Expression of cytokines, T- and B-cell receptor components, chemokines, and signal transduction elements within the cell. Chemokine genes and their ligands associated with these processes are overexpressed: CCR2, CXCL13, CXCL11, CD1C, CXCXL10, CCL5.

Luminal - AR subtype (LAR, cluster B) is associated with activation of androgen and estrogen biosynthesis.

Mesenchymal Subtype (MES, cluster C) is associated with process activation in extracellular matrix components and is characterized by overexpression of the TGF-b signaling pathway.

Basal-Like Immunosuppressive Subtype (BLIS, cluster D), unlike mesenchymal subtype, is characterized by hyperactivation of cell proliferation processes, which is caused by overexpression of a number of regulatory genes: CENPF, BUB1, PRC1. In this subtype, the processes of regulating the immune response are severely suppressed [31].

Despite advances in tumor characterization, each classification is not yet appropriate for the specific treatment, except for PARP inhibitors or platinum preparations in carriers of BRCA1/2 germline mutations and possibly in the near future inhibition of immune checkpoints in tumors with PD-L1-positive immune cells [32]. Nonspecific systemic chemotherapy, as used to treat TNBC, is frequently associated with untargeted tissue toxicity and drug resistance. Surgery and radiation therapy have also been used to treat TNBC. Because of the poor prognosis, 67% and 33%, respectively, have mastectomy in the case of TNBC rather than organ-sparing surgery [4]. Until recently, radical mastectomy was the main surgical operation in TNBC. In addition to the oncological radicalism, the cosmetic result of the operation is of great importance, which is especially important due to the younger age of patients with TNBC, given the impact on the quality of life of patients. In this aspect, the development of breast oncological surgery took place in two main directions: Reducing the indications to BC in favor of organ-conserving operations and the development of reconstructive and restorative operations.

The arsenal of surgical treatments for BC is quite wide. A common trend in recent years has been a combination of plastic surgery and oncology - increasing the proportion of skin-preserving mastectomy with plastic surgery of own tissues or endoprostheses and abandoning extensive lymph dissections in favor of sentinel lymph node biopsy. It should be noted that the choice of surgical procedure depends on the decisions of the surgeon and the patient [33].

The ability to personalize treatment to each patient is particularly important in this group because of the high risk of long-term recurrence and death. Defining molecular genetic subtypes and identifying targets for personalized therapy may help broaden the spectrum of drugs, increase survival, reduce locoregional metastasis, and improve disease surveillance.

This review summarizes the existing strategies for managing triple negative breast cancer, with a focus on a personalized approach to patient management.

Recent clinical guidelines consider the following drugs for treatment of TNBC.

Cytotoxic chemotherapy

TNBC shows initial susceptibility to cytotoxic chemotherapy. However, in most cases, the response rate is higher than for other subtypes of breast cancer. About 40% to 50% of TNBC cases achieve a pathologic complete response after treatment with a sequential regimen of anthracyclines and third-generation taxanes. A complete abnormal response is a reasonable predictor of improved prognosis for disease-free and overall survival after neoadjuvant chemotherapy for the TNBC subtype [34].

Anthracyclines and Taxanes

Anthracyclines target the cell proliferation pathway, leading to double-strand breaks in DNA.

Taxanes disrupt cellular spindle formation and delay G2 and M phases of mitosis. Drugs in this group (paclitaxel and docetaxel) are routinely used to treat the early stage of TNBC.

Braybrooke et al. meta-analysis data. 2021 This study showed a 10-year decrease in recurrence risk of 18% with anthracycline added to taxane chemotherapy compared with taxane alone [35].

Patients with cancer types BL1 and BL2 appear to have a better response to this class of drug [36].

Advantages of neoadjuvant CT include: Shrinking the tumor size, leading to the possibility of organ-saving surgery, and as a result, reducing postoperative complications and improving cosmetic effect. In addition, the results of a pathological examination of the post-operative material allow to estimate the potential response to treatment at an early stage and provide valuable prognostic information [37].

Cyclophosphamide: Cyclophosphamide, one of the successful chemotherapy drugs, is used to treat some cancers, such as lymphomas, breast and ovarian cancers, in both adjuvant and neoadjuvant therapy [3].

Cyclophosphamide belongs to the group of drugs – alkylating agents. The mechanism of action of this subgroup of drugs is determined by the fact that they have the ability to attach to many substances through alkylation. That is, there is a substitution of the hydrogen atom of any compound for an alkyl group. As a result, DNA replication is disrupted, mutations occur, and cell death occurs [38,39].

Platinum agents: Platinum cytotoxic agents disrupt DNA synthesis through intra- and interstrand DNA cross-linking as well as binding to cell membranes [39]. Platinum agents (such as cisplatin, carboplatin) are more effective in tumors with impaired DNA repair pathways (a finding commonly seen in basal-like 1 TNBC), as well as in patients with hereditary mutations such as BRCA and other homologous recombination pathways [34].

In theory, BRCA mutant cells are sensitive to DNA-damaging agents such as platinum agents. Carboplatin has been shown to be effective in metastatic TNBC with germline BRCA mutations. Chemotherapy for patients with early breast cancer with BRCA mutations is still controversial because the effect of platinum supplements on neoadjuvant and adjuvant therapy is unclear. Several studies have demonstrated that patients with BRCA mutations have achieved higher pCR values with a platinum neoadjuvant [40].

In the CALGB 40,603 [41] and BrighTNess studies, patients with early-stage BC had higher pCR values when carboplatin was added [42]. A meta-analysis of nine randomized controlled trials confirmed a significant increase in the incidence of RWP with platinum-based neoadjuvant therapy (52.1% *vs.* 37.0%, p<0.001) [43].

In general, the role of platinum chemotherapy in TNBC is now largely limited to neoadjuvant therapy outside of clinical trials.

However, regimens of eribulin + carboplatin and paclitaxel + carboplatin have been reported to be effective in the localized TNBC stages T1N1-3, T2-4N0-3 in the literature. The study included 61 patients. All patients received Neoadjuvant polychemotherapy under 2 different regimens: The first group of patients were treated with eribulin 1.1 mg/m^2 chemotherapy during the 1st and 8th day of the 21-day cycle combined with AUC6 carboplatin; the second group of patients were treated with paclitaxel 80 mg/m^2 chemotherapy during the 1st and 8th day of the 21-day cycle combined with AUC6 carboplatin. 24 patients in the 1st group and 27 patients in the 2nd group underwent surgery at various levels [44]. The rate of Complete pathomorphologic Regression (ypCR) in group 1 was 8 (33%) *vs.* 16 (60%) in group 2. TNBC has been known to be more sensitive to platinum preparations, particularly in the presence of the BRCA1 mutation [45].

Antimetabolites: Antimetabolite anticancer activity is based on structural or functional similarity to their metabolites, which are involved in nucleic acid synthesis. The recognition and exchange of antimetabolites in the tumor cell results in the malfunction of enzymes involved in nucleic acid synthesis. It is also possible to incorporate antimetabolites into nucleic acids, which leads to the violation of their code, and causes cell death. Because the application point is DNA synthesis, antimetabolites are most active in fast-growing cells and are mostly phase-specific drugs.

Capecitabine: A systematic review and meta-analysis of capecitabine use in neoadjuvant and adjuvant therapy showed a significant increase in both recurrence-free survival and overall survival in early-stage TNBC patients with intolerable adverse events. (HR (Hazard Ratio) 0.75, 95% CI (Confidence Interval) 0.65-0.86, p<0.001), and overall survival (HR=0.63, 95% CI 0.53-0.77, p<0.001).

Capecitabine regimens have been associated with higher risk of diarrhea (HR=2.88, 95% CI 2.23-3.74, P<0.001), stomatitis (HR (odds ratio) = 2.01, 95% CI 1.53-2.64, P<0.001), and hand and foot syndrome (HR) = 8.67, 95% CI 6.70-11.22, P<0.000 1) [46].

Immunotherapy

Atezolizumab and Pembrolizumab are drugs that inhibit immune checkpoint pairs, Programmed Cell Death-1 (PD-1), and Programmed Cell Death Ligand 1 (PD-L1), which are expressed on T cells and breast cancer cells respectively.

The addition of pembrolizumab to neoadjuvant therapy has shown an increase in the total pathological response rate in several studies, including KEYNOTE-173 and I-SPY 2 [47].

Atezolizumab in combination with nab-paclitaxel is the 1st-line treatment standard for PDL-1-posi-tive (SP 142, more than 1% on immunocompetent IC cells) mTNBC. Pembrolizumab is another drug in this group that has been studied in mTNBC. It was previously approved by the U.S. Food and Drug Administration (FDA) as the first drug with Microsatellite Instability (MSI) regardless of tumor location. There were few patients with mTNBC in the registration study, and intensive pre-treatment patients were included [48].

With the addition of atezolizumab to anthracycline/taxane-based chemotherapy, the rate of complete pathological response improved from 41% to 58% in Impassion03 [49].

PARP inhibitors

Prevalence of BRCA germline mutations ranges from 1.2% to 8.8% in the populations of patients with breast cancer and 15% with TNBC. The *BRCA1* and *BRCA2* genes encode proteins critical to the repair of double-stranded DNA breaks in the process homologous recombination. Poly(ADP-ribose)-Polymerase (PARP) enzymes play an important role in maintaining genome stability to resolve stopped replication forks, detect double-stranded DNA breaks, and ensure that additional DNA repair factors are involved in dam-aged DNA damage. Thus, targeting the DNA damage response pathway can be used clinically as an attractive strategy to destabilize tumor genomic integrity and trigger genomic catastrophe and cell death. Patients with BC disease with germ BRCA1/2 mutations respond favorably to DNA repair therapies such as platinum salts and PARP inhibitors [50].

Oncologists have two drugs that act on the enzymes poly(ADP-ribose) Polymerase (PARP), which they use in BRCA1/2 mut TNBC olaparib and talazoparib [51].

Conjugated drug

Metastatic BC is treated with the drug Sacituzumab govitecan, a conjugate formulation in which a targeted element is antibody to the Trop-2 antigen (trophoblastic cell surface antigen 2). Because the drug was highly effective, he received expedited FDA approval in April 2020. Shortly before this, the Phase III ASCENT trial was terminated prematurely due to the superior efficacy of the investigational drug. Clinical efficacy was 45.4%. Results from the two studies were considered a breakthrough in mTNBC therapy and were included in clinical recommendations for treatment of mTNBC following the drug's registration [48].

PI3K/AKT/mTOR pathway inhibition

The PI3K/AKT/mTOR pathway is often activated in processes involved in oncogenesis, cancer cell proliferation, survival and resistance to anti-tumor therapy. It is also critical in TNBC because PI3K or AKT1 mutations and activation and loss of PTEN are common in TNBC. The incidence of genomic changes in PI3K is second only to TP53 in TSIT, but they are much less common (~10%) in TSIT than in other subtypes of breast cancer (34.5% in HR+ RGM and 22.7% in HER2+ BC). Incidence of PIK3CA mutation is higher in residual TNBC and AR-positive TNBC, whereas AKT3 amplification and PTEN deletion are increased in the basal subtype. Patients with TNBC with the PIK3CA mutation have a higher median OV after focused treatment than those with TNBC of the wild type PIK3CA. Inhibitors of this pathway, such as ipatasertib (an AKT inhibitor), buparlisib (a PI3K inhibitor), everolimus (a mTOR inhibitor), and capivasertib (an AKT inhibitor), have been evaluated for their anti-tumor effects in clinical trials [52].

PI3K-AKT inhibitors

Another strategy for further research may be to investigate PI3K/AKT pathways for triple negative breast cancer. This pathway may be mis-regulated in TNBC. This may be due to mutation activation in PI3KCA or loss of PTEN function and/or Proline-rich Inositol Polyphosphatase (PIPP).

The PIK3CA gene can be mutated in 16% of primary TNBC, and mutations in PIK3CA reduce tumor cell growth factor dependence, facilitating cell growth and transformation. Current studies suggest that patients with a mutation that enhances PIK3CA are less likely to achieve pCR than those with wild-type PIK3CA tumors, suggesting that PI3K inhibitors may increase chemotherapeutic sensitivity. However, it has been shown that this association depends on the specific type of PIK3CA mutation and Neoadjuvant chemotherapy mode [53].

Alpelisib is a selective inhibitor of the Catalytic Alpha subunit PI3K (PIK3CA) and has been registered for the treatment of metastatic HR+/HER2-mutant breast cancer with PIK3CA in conjunction with endocrine therapy. About 50% of patients with TNBC have some variation in the PI3K pathway, making them a potential target for treatment with alpelisib and other PI3K inhibitors. A study that combined alpelisib with nab-paclitaxel for HER2-negative breast cancer reported an objective response rate of 59% and a median progression-free survival rate of 8.7 months. In this study, TNBC was found in 30% of patients. Based on these results, the EPIK-B3 study was developed to investigate the possibility of adding alpelisib to chemotherapy in patients with advanced TNBC and PIK3CA mutations or loss of PTEN.

Further strategies for the development of treatment of TNBC

Vascular Endothelial Growth Factor (VEGF) is an important angiogenic factor. VEGF promotes tumor cell proliferation, has an antiapoptotic effect on endothelial cells, and promotes the formation of new vessels in breast cancer. The VEGF family includes glycoproteins that stimulate the formation of new blood and lymphatic vessels and increase vascular permeability. The family includes 6 growth factors: VEGF-A; VEGF-B; VEGF-C; VEGF-D; VEGF-E and Placental Growth Factor (PLGF). One of the activators of VEGF is Hypoxia-Induced Factor-1 (HIF-1).

Patients with TNBC have significantly higher VEGF levels and shorter disease-free survival and overall survival than patients without TNBC.

Bevacizumab, a recombinant humanized monoclonal antibody against VEGF-A. In 2004, it was approved by the FDA for use in combination therapy regimens for the treatment of metastatic colorectal cancer. According to clinical studies, the efficacy of bevacizumab and generally good tolerance as a VEGF inhibitor make it promising as a stand-alone treatment or as part of combination regimens for breast cancer. It is also important to note that the addition of this drug may increase adverse effects such as hypertension, neutropenia, and mucositis. Two large randomized trials demonstrated a significant increase in the incidence of pathologic complete response in HER2-negative patients when

bevacizumab was added to neoadjuvant chemotherapy, and efficacy was limited mainly to patients with TNBC. Several studies have also shown mixed results. The GeparQuinto study examined the pCR effect of adding bevacizumab to standard neoadjuvant chemotherapy, and the results showed a higher pCR rate in the group treated with bevacizumab, especially in patients with BRCA gene mutations. However, the BEATRICE trial showed no significant improvement in disease-free or overall survival. The heterogeneity of the TNBC subtypes may cause these different results, and bevacizumab may respond differently to the molecular subgroups. The potential of bevacizumab and its effect still require further monitoring [4].

Further development of new PARP inhibitors as well as combinations with other drugs may be a part of the strategy to develop therapy for triple negative patients.

Many other PARP inhibitors are in different stages of clinical trials. Fluzoparib (a PARP1 inhibitor) has been tested in combination with camrelizumab (a PD-1 inhibitor) and apatinib (a VEGFR inhibitor) in NCT03945604 (phase I) with evidence of efficacy, particularly in patients with BRCA1/2 mutations in patients with relapsed or metastatic TNBC [51,54].

Another phase I drug, veliparib, has shown efficacy in patients with SIT, either as monotherapy or when combined with other drugs. Veliparib can be used safely and tolerated with a continuous schedule of 400 mg twice a day, and this treatment is associated with clinical activity in BRCA mut and BRCA-wt patients [55].

Targeting the Androgen Receptor (AR)

Another promising development in drug treatment of HMVR is therapy directed at androgen receptors.

The AR expression on TNBC occurs in patients over age 61 with locally advanced disease. It is characterized by multifocal tumor growth, high differentiation, and low proliferative activity [24].

Among the molecular subtypes of TNBC, the Luminal Androgen Receptor (LAR) is characterized by pattern gene expression similar to that of luminal cancer. Compared with other subtypes of TNBC, LAR TNBC has high androgen receptor expression as per IGS assays and is rich in activation of the PIK3CA or AKT1 mutations. The clinical benefit of monotherapy with antiandrogens in patients with unselected TNBC or in subgroups defined by biomarkers is determined by RA IHC [56]. Clinical efficacy of bicalutamide or enzalutamide ranges from 19% to 35%. Several important studies are under way to determine the role of RA blockade. One is a phase 3 trial comparing the addition of bicalutamide to chemotherapy for AR+ mTNBC [NCT03055312]. In addition, as with luminal carcinoma, PI3KA/AKT inhibitors are investigated for LAR subtypes of TNBC. In the phase 2/3 TBCRC 032 trial, the PI3KA inhibitor taselisib was combined with the RA blocker enzalutamide. Clinical efficacy for the LAR subtype was 75% compared to 12.5% for non-LAR tumors. Alpelisib with enzalutamide is ongoing [NCT03207529], and in a study combining CDK4/6 inhibitor, palbociclib, with enzalutamide, the median of 6-month EBP was 33% in the primary analysis [57].

Conclusion

TNBC is no longer a single nosological group but should be divided into subgroups based on criteria: Heterogeneous molecular structure, different survival rate, and different response to treatment. Proper selection of subgroups of patients with TNBC is critical to determine the best treatment approach.

Basal-like subtype 1 has shown to respond better to neoadjuvant therapy.

Basal-like subtype 2 is more commonly associated with BRCA1/2 mutations and already has application points for PARP inhibitors.

Mesenchymal subtype has a high expression of PD-L1, allowing for the use of immune drugs.

LAR tumors exhibit an extremely high sensitivity to the antiandrogenic nonsteroidal drug bicalutamide.

Thus, depending on the molecular profile of TNBC, various subtypes are distinguished, the diagnosis and treatment of which today require further in-depth study.

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