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"Triple Negative Breast Cancer: Prognostic Biomarkers, Genetic Influences, And Recent Advances In The Treatment"

[1]Minakshi Joshi, [1]Dr.Ajay Kale, [2]Aditya Pardeshi , [2]Jay Munjal,[2]Omkar Kapse,[3]Deepak Kumar

[1]Department Of Pharmacology, Navsahyadri Institute Of Pharmacy, Pune, India
[2]Department of Pharmaceutical Sciences and Technology, Institute of Chemical Technology (Elitestatus), Mumbai,India
[3]Department of Biological Science and Biotechnology, Institute of Chemical Technology,Mumbai, India

[1] Department Of Pharmacology, Navsahyadri Institute Of Pharmacy, Pune, India
[1]Navsahyadri Institute Of Pharmacy , Pune, India

Abstract: Triple-negative breast cancer (TNBC) is the most aggressive subtype of breast cancer, accounting for 15% of occurrences worldwide. It is identified by the simultaneous lack of HER2, the progesterone receptor, and the estrogen receptor. Because it precludes the use of effective medications like hormone treatment and anti-HER2 medicines, this feature makes TNBC extremely aggressive and difficult to treat. In this review, we examine established treatments as well as more recently developed strategies for TNBC, such as immune checkpoint inhibitors, PI3K/AKT pathway inhibitors, cytotoxin-conjugated antibodies, and PARP inhibitors. The present state of mainstream therapeutics for this condition is contextualized to provide a pragmatic and prospective explanation of the medications' mechanism of action and their use in clinical practice.These developments offer a promising new area for customized therapies that could significantly enhance TNBC patients' results. It's interesting to note that although TNBC presents a difficult issue, it also acts as a paradigm and a chance for translational research and cutting-edge cancer treatments.

Keywords- Triple-negative breast cancer ; Prognosis ; PARP inhibitors ; Immunotherapy; chemotherapy; limitations.

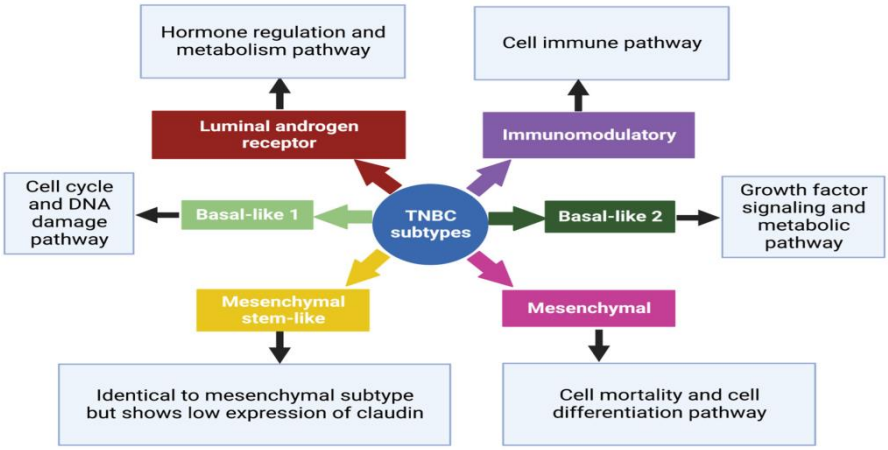
INTRODUCTION

The most aggressive subtype of breast cancer (BC), recognised as triple-negative breast cancer(TNBC), is distinguished through the simultaneous loss of receptor for human epidermal growth factor 2 (HER2, CD340), progesterone receptor (PR), and estrogen receptor (ER) [1]. TNBC diagnoses account for 15% or so of all BC cases worldwide. Unfortunately, the lack of all three receptors at the same time restricts the availability of focused molecular medicines, which makes treatment difficult. For many patients, therefore, standard and possibly harmful treatments continue to be the cornerstone of their care. A noteworthy worry that adds to the heightened death risk linked to TNBC is the more frequent recurrence following aggressive procedure when in contrast to other varieties of BC [2]. Particularly when it comes to invasive ductal carcinoma, apocrine carcinoma, metaplastic carcinoma, and medullary carcinoma, TNBC cases typically have high histological grade and fast proliferation.. Generally speaking, low-grade neoplasms include uncommon histological subtypes such secretory carcinoma and cancer of the adenoid cystic type of the salivary glands [3]. Germline Mutations in BRCA1/2 are frequently more prevalent in patients with TNBC [4].Moreover, in comparison to other subtypes, this specific tumor subtype is linked to a higher concentration of lymphocytes infiltrating

tumours [5]. In contrast to other BC subtypes, TNBC's survival curves indicate a rise in relapses over the first three to five years following diagnosis, followed by a decline in survival. Technological developments in transcriptomics have made it easier to identify a number of molecular drivers that characterize seven different clusters found in triple-negative breast cancers (TNBCs): immunomodulators (IM),receptor for luminal androgen (LAR), like mesenchymal (M), stem-like mesenchymal (MSL), and erratic clusters. The expression of genes linked to DNA repairing and cell cycle control in the underlying gene cluster characterizes BL1. BL2 exhibits a phenotype that is extremely proliferative, similar to BL1 and a noticeable upregulation of markers of myoepithelial differentiation as well as genes implicated in growth factor signaling. The low intrinsic claudin subgroup is primarily shared by the M and MSL subtypes, which exhibit augmentation of genes encoding mesenchymal differentiation, invasion, and cell motility regulators. In addition, MSL and type IM share a large number of genes that control immunological reaction, presentation and processing of antigens, and immune cells activity, and mechanism of cytokine signaling. In addition to having a increased incidence of lobular histology that is invasive,tumours that are categorised as LAR variants frequently exhibit changes in the increased levels of androgen receptor (AR) expression, including PI3K pathway gene, neurofibrosis type 1 (NF1), serine/threonine-protein kinases (AKT1), phosphatidylinositol 3-kinase catalytic subunit alpha (PI3KCA) (55%), and cadherin 1 (CDH1) (13%) among others. Moreover, Lehmann et al. observe that specific features across subtypes with respect to presentation and result are correlated with the presence of unique stromal cells. Following this discovery, TNBC was reclassified into four subgroups: M (which includes the majority of MSLs), BL1 (immuno-activated), and BL2 (immuno-suppressed) [7]. Fascinatingly, the specific subtype of TNBC has a major impact on the reaction to chemotherapy given neoadjuvantly (NACT); the LAR subtype reports the lowest rates of pathologic complete response (pCR) at 21.4%, while the BL1 subtype reports the greatest at 65.6%.[8] Although the advancement in next-generation sequencing has made it feasible to identify targets that may be treated, there has been little implementation of these findings in ordinary clinical practice for individuals with TNBC who are not picked. Limited efficacy has been demonstrated by numerous targeted therapeutic techniques throughout clinical trials., However, molecular subtyping makes it possible to identify discrete groups that share mutations in their genomes, providing a means of targeting clinical investigations according to subtype and creating more effective medication regimens. Transcriptomic subtyping for TNBC patients must therefore be incorporated into a precision medicine framework that is established and refined. This strategy has the potential to enhance personalised care.[9]

Subtypes of TNBC

TNBCs often share characteristics of gene expression with basal-like breast cancer (BLBC) [10]. Six TNBC subtypes —biomodulatory subtype (IM), mesenchymal subtype (M), mesenchymal stem-like subtype (MSL), basal-like 1 (BL-1), and basal-like 2 (BL-2), The gene expression profiles were used to identify the luminal androgen receptor subtype (LAR).[11,12]. Each subtype posseses a distinct profile of gene expression and ontology. In spite of this, Vimentin, EGFR, basal cytokeratin, and and mutant BRCA1/2 gene are among the hallmarks of basal-associated malignancy that the majority of triple-negative breast tumors (80%) express [13]. The genetic differences between these TNBC subtypes point to the need for tailored treatment as opposed to a broad strategy.[14]



TNBC subtypes and their distinctive routes. Six TNBC subtypes have been identified based on gene expression profiles; each has a unique gene expression profile and ontology.[28]

1.Basal-like 1 and 2 Subtypes

TNBC is primarily composed of basal-like subtypes, accounting for approximately 75% of the total. The basal-like 1 subtype exhibits a high degree of reaction to DNA damage. As stated by research, Immunosuppressive subtypes of TNBC that are basal-like show reduced levels of B cells, T cells, and a poorer prognosis due to natural killer cells.In general, every BRCA1/2 mutation is linked to genes with basal-like patterns. HER2 and anti-ER treatments are ineffective for breast tumours resembling basals as In addition, neither protein is usually conveyed[15,16]. This subtype of TNBC exhibits increased DNA damage response (DDR) gene expression, chemotherapeutic sensitivity, and cell cycle related genes [10,14]. Studies similar to basal-like subtypes with increased cell cycle and DNA damage response levels genes are susceptible to platinum-containing medications (cisplatin), The BL-1 subtype, however, is sensitive to PARP inhibitors [17-20].

2. Subtype of Luminal Androgen Receptor

The androgen receptors in the luminal control steroid and porphyrin synthesis, as well as androgen and estrogen metabolic processes. Expression of AR is linked to a high survival rate in TNBCs. AR is thus a predictive metric. This subclass expresses androgen receptors 10 times more than other subtypes. Recent studies indicate that AR inhibitors may benefit AR-positive TNBC patients [15, 21].

3.Mesenchymal and Mesenchymal Stem-like Subtypes

The stem-like mesenchymal subtype interferes with receptors for G-proteins, EGFR, and calcium signalling, in addition to other Pathways that affect differentiation and cell motility.It is characterized by increased expression of STAT genes, which are In charge of producingNatural killer cells, B-cells, and T-cells. Alterations to the M subtype affect the interaction of ECM receptors. The M subtype includes metastatic-to-epithelial transition (EMT) and cancer stem cells [22]. In mesenchymal and MSL cell lines, inhibition of PI3K/mTOR and non-receptor tyrosine kinase (Src) inhibited the growth factor pathways and the epithelial-mesenchymal transition (EMT).[17].

4.Subtype of Immunomodulation

This subclass resembles a subtype similar to basal. The prognosis for this subclass is positive, however the histology the rating is high. These subclass evade the immune system because of immune cell signalling overload. Tumours may bypass the immune system by enlisting the help of immunological suppressor cells or turning on immune checkpoint molecules making immune checkpoint blockage a viable treatment option [14].

Prognostic Biomarkers

Establishing prognostic indicators for TNBC is crucial for developing targeted treatments. Several indicators can predict TNBC outcome, including cathepsin D, node state, and Ki67 index, BRCA1, p53 and the value of promoter methylation. These genes regulate cell invasion (cathepsin D), differentiation (pS2, ERα, and PgR), cell death (p53), and proliferation (c-erbB-2 and c-erbB-3).[23]. TNBC has increased levels of VEGF, TILs, and TAM [24]. Predictive techniques can accurately estimate rates of both overall and disease-free survival in TNBC individual. If there is a bad prognosis, alternative management approaches may be examined [11]. In modern malignancy studies, Treating TNBC can involve systemic immunotherapy because this kind of cancer has been shown to have immune response, as demonstrated by prognostic and predictive stromal tumor-infiltrating lymphocytes (STILs). Individual with TNBC also have a elevated concentration of lymphocytes invading tumors. [25], which have been proved to be accurate prognosticators. TNBC has consistently higher TIL levels than other subtypes, which are related with improved survival [26]. In lymphocyte-predominant breast tumors, the pathological complete response (pCR) rate was 40%, while in non-lymphocytic malignancies, it was 7%. [24, 25]. Research involving checkpoint inhibitors [27] have proven the importance of assessing immunological markers in TNBC. TILs, especially in TNBC, are prognostic and predictive.[28].Triple-negative characteristics, p53 mutations, and a high mitotic Index were present in breast cancers linked to BRCA1. [29, 30]. Using a BRCA1 murine mammary epithelial cell (MMEC) model, Alli et al. examined how cellular susceptibility to different chemotherapeutic treatments was

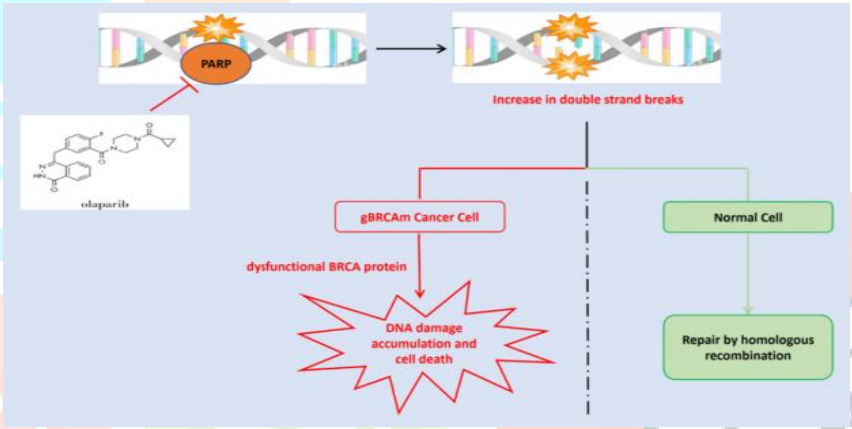
affected by BRCA1 gene deletion. For BRCA1-deficient MMECs, cisplatin and gemcitabine are effective treatments, even though they are not part of first-line regimens for breast cancer. Nevertheless, common therapies for breast cancer, such as docetaxel, paclitaxel (PTX), 5-fluorouracil, and doxorubicin, were effective.[31]. In TNBC, the tumor mutational burden (TMB) is comparatively elevated. Around 60 somatic mutations are present in each megabase (Mb) of coding region in a TNBC. TNBC has a disparate mutation burden, with certain tumors having over 4.68 per mb somatic mutations and several copy-number inconsistencies affecting multiple pathways. For some types of cancer, TMB may function as a TNBC biomarker. Through the promotion of neoantigen production and presentation, TMB enhances the immune response. Due to a lack of clinical evidence, TMB is not being widely used. Pembrolizumab for cancers with increased TMB was recently approved by the FDA. [24]. It is important to consider AR expression while evaluating ER, PR, and HER2 status, especially in African American women, as it is linked to a high survival percentage in TNBC.[22].

BRCA1 and 2 genes function and role in breast cancer

There are several methods by which the DNA that has been destroyed by internal or external events in cells is restored. These consist of DSB repair, mismatch repair, nucleotide excision repair, and BER. Specifically, non-homologous end joining and homologous recombination that takes place during the S and G2 phases of the cell cycle are included in DSB repair. The integrity and functionality of DNA are restored by these repair mechanisms [32]. The tumor-suppressive genes BRCA1 and BRCA2 have high penetrance and an autosomal dominant inheritance pattern. These genes encode proteins that are necessary for homologous recombination repair (HRR), a conservative form of DNA repair that attempts to fix the original DNA sequence in response to DNA double-strand breaks (DSB). BRCA1 contributes to the elimination of tumor DNA ends, an essential step in HR. By unwinding DNA ends and producing single-stranded DNA overhangs, it activates the MRN complex. As a result, nucleoprotein fires are produced when Rad51 loads onto ssDNA. As a mediator, BRCA2 aids Rad51 in overcoming inhibitory factors. Rad51 and ssDNA interact with BRCA2. It promotes strand invasion and stabilizes the Rad51-ssDNA complex. In order to match the damaged strand with an intact homologous DNA template, Rad51 looks for homologous sequences. This results in the formation of a D-loop structure, where DNA synthesis starts with the intact template and ends with the DSB being repaired.[33]. BRCA1/2 dysfunctions can be caused by germline mutations, enhancer methylation, or somatic changes. This study cannot fully explain specific BRCA1 and BRCA2 mutations. For more information, please refer to other sources [34, 35]. The BRCA1/2 genes have more than 2000 mutations. Remarkably, these genes show different patterns of mutation and are located on different chromosomes (17 and 13, respectively). Through nonsynonymous truncations, splice site disruptions throughout its exons, and minor insertion/deletion frameshifts, BRCA1 mutations result in nonfunctional proteins. Approximately one-third of BRCA1 mutations are caused by large genomic rearrangements (LGRs), which can occur through homologous recombination among the BRCA1 gene and other genes.and pseudogene sequences [36]. The bulk of BRCA2 gene mutations occur in exons 10 and 11, creating missense changes and premature end codons, which result in nonfunctional proteins. The C-terminal region contains critical domains for BRCA2 activity, including as the Double Strand Break Domain (DBD), Nuclear Localization Signal (NLS), and Rad-51 Binding Motif [37]. BRCA1/2 mutations exhibit population-specific patterns, with studies identifying distinct variants across multiple populations [38, 39]. Mutations affecting BRCA1/2 or other HR systems result in genomic instability [40].Furthermore, patients with deleterious BRCA1/2 mutations are more vulnerable to alkylating agents, platinum salts, and poly ADP-ribose polymerase inhibitors. These compounds selectively cause irreparable DNA damage in HR-deficient cells, leading to cell cycle halt and apoptosis.[41]. Germline mutations in BRCA1/2 are associated with 52% and 32% of cases, respectively, of hereditary breast malignancies [42]. Approximately 10% to 20% of people with TNBC, particularly those under the age of 60, have these mutations often [43]. BRCA1 mutation carriers with TNBC diagnoses range in median age from 47.2 to 58.8 years; they are often younger than BRCA2 carriers. [44]. Research indicates that the frequency of BRCA1/2 mutations in germline varies according on race/ethnicity. Asians have the lowest occurrence at 0.5%, whereas Ashkenazi Jews have the greatest at 10.2% (source: [45]). A recent study in the US found that the AJ population has a greater rate of harmful BRCA2 mutations in contrast to white non-Hispanics. However, race or ethnicity has no effect on BRCA1 alterations.[46].

Current standard chemotherapy for TNBC

Triple-negative breast cancer has historically had fewer treatment options than other kinds of breast cancer. Despite the emergence of innovative targeted medications, cytotoxic chemotherapy with anthracyclines and/or taxanes remains the standard treatment for TNBC. Chemotherapy has been shown to be more effective in treating TNBC in neoadjuvant, adjuvant, and metastatic settings, with higher pathological response rates compared to HR+ BC [47]. The general prognosis of TNBC is dismal, despite its chemosensitivity [48]. With pCR rates thirty to forty percent greater than in other breast cancer subtypes, neoadjuvant systemic treatment is currently the cornerstone of care for early-stage TNBC [49]. Notably, improved survival outcomes have been associated with achieving pCR with main therapy [50]. Because it indicates positive long-term results in TNBC, pCR is a reliable endpoint in clinical trials assessing the effectiveness of neoadjuvant chemotherapy. The neoadjuvant chemotherapy treatment, however, consists of paclitaxel, cyclophosphamide, and adriamycin because of the heterogeneity of TNBC. This usual regimen has proven to be highly effective, with pCR rates ranging from 35 to 45% [51].The NCCN guidelines advocate systemic chemotherapy regimens for treating TNBC. Treatment options include docetaxel and cyclophosphamide (DC), taxanes, adriamycin, and cyclophosphamide (TAC), adriamycin and cyclophosphamide (AC), cyclophosphamide, methotrexate, and fuorouracil (CMF), cyclophosphamide, adriamycin, and fuorouracil (CAF), and cyclophosphamide, epirubicin, and fuorouracil. Chemotherapy medicines that cause DNA damage have shown increased efficacy in cancers with germline BRCA mutations [52].



Schematic representation of the action of PARP inhibitors, leading to divergent outcomes based on cell origin. In cancer cells, PARP inhibitors induce cell death, while in healthy cells, they promote repair through recombination mechanisms

Platinum-based chemotherapy has been recommended as an additional treatment option. Tumor cells are more vulnerable to platinum therapies in the absence of functional BRCA proteins [53].Nevertheless, regardless of the presence of germline BRCA1/2 mutations, two sizable randomized clinical studies have demonstrated that adding platinum to NACT regimens increases pCR rates for TNBC. The CALGB 40603/Alliance trial evaluated the addition of bevacizumab and carboplatin to neoadjuvant chemotherapy and included 443 patients with stage II and III TNBC. The patients were administered 80 mg/m2 of paclitaxel once a week for 12 weeks. Thereafter, they got 60 mg/m2 of doxorubicin and 600 mg/m2 of cyclophosphamide every two weeks for four cycles. To decide whether patients would receive wP with or without concurrent carboplatin at an area-under-the-curve (AUC), random assignment was carried out. For four weeks, take a dose of six every three weeks. Patients were randomly assigned to receive 10 mg/kg bevacizumab every two weeks for nine cycles, alternating between wP and ddAC for the first three cycles. Examinations took place every 2-3 weeks. Patients who progressed on wP were moved to ddAC, but progression during ddAC treatment necessitated immediate surgical intervention. Carboplatin increased the proportion of patients who achieved pCR from 41 to 54% in the GeparSixto study (OR=1.71; p=0.0029) [54]. There were 595 participants in stages II or III of the study. Individuals diagnosed with Stage III TNBC were randomized to either carboplatin or no carboplatin in conjunction with baseline therapy (paclitaxel: 80 mg/m2 intravenously every week for eighteen weeks; non-pegylated liposomal doxorubicin, Myocet®: 20 mg/m2 every week for eighteen weeks; trastuzumab, exclusively for HER2-positive patients: loading dose of 8 mg/kg, maintenance dose of 6 mg/kg, day 1 q day 22, for six cycles). With rates of 53.2% versus 36.9% (P=0.005) in the non-carboplatin group, the

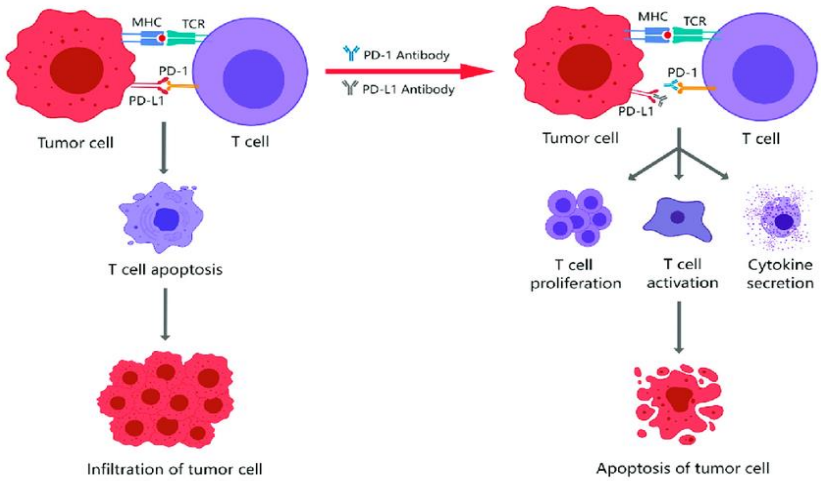
pCR rates were considerably higher in the carboplatin group.[55].Adding platinum to neoadjuvant chemotherapy significantly enhances pCR rates, increasing from 37.0 to 52.1% (OR 1.96, 95% confidence interval (CI) 1.46-2.62, P<0.001), according to a meta-analysis of nine randomized controlled trials (RCTs) involving 2109 people. [56]. Concurrently, in 2018, the TNT trial—a phase III trial—was conducted. In 376 patients with metastatic TNBC, the trial assessed the efficacy of carboplatin in comparison to the standard treatment of docetaxel 100 mg/m2. In the carboplatin and docetaxel groups, the overall response rate (ORR) was comparable, at 31.4% and 34.0%, respectively. Additionally, there was no discernible difference in the median overall survival (OS) or progression-free survival (PFS) between the two therapy groups. PFS was found to be 3.1 months (95% CI 2.4-4.2) in the carboplatin group and 4.4 months (95% CI 4.1-5.1) in the docetaxel group (P = 0.40). The median overall survival (OS) for carboplatin was 12.8 months (95% CI 10.6-15.3), while the median OS for docetaxel was 12.0 months (95% CI 10.2-13.0) (P = 0.96). A statistically significant difference in ORR was seen between the groups receiving carboplatin treatment (68%) and docetaxel treatment (33.3%) among the 43 patients with germline BRCA1/2 mutations. Carbaplatin considerably raised the median PFS (6.8 months) in BRCA-mutant patients as compared to docetaxel (4.4 months) (P = 0.002).The OS evaluations did not show any discernible changes. As anticipated, both drugs had good safety profiles.. BRCA-mutated individuals did not benefit from BRCA1 methylation, low tumor mRNA levels, or high HRD scores [57]. The trial found that carboplatin had equivalent therapeutic benefits to docetaxel and a lower toxicity profile, making it a feasible choice for treating metastatic TNBC [58].

Advancements in Immunotherapy.

Breast cancer can now be efficiently treated using immunotherapy in combination with surgery, adjuvant chemotherapy, and radiation therapy.[59]. Immunotherapy, with a focus on immune checkpoint inhibitors (ICIs), entails provoking the immune system to mount an anticancer response. ICIs, or immune-modulating compounds on the cell surface, have shown promise as a possible TNBC treatment because they alter the immune system, including T-cell activation. ICIs have a unique ability to control autologous cells, avoiding excessive immune activation and maintaining immune system activity within normal bounds. Research has demonstrated varying levels of effectiveness, from no effect to a modest effect. A few studies have even demonstrated an increase in pathological complete response (pCR) in early stage TNBC.ICIs lessen the damage that infectious microorganisms inflict to tissue and autoimmune. [60, 61]. Therapeutic approaches for TNBC have significantly advanced as a result of research on inhibitory chains (ICIs). These drugs have the ability to reduce immunosuppression and increase T-cell antitumor activities, which may improve overall survival rates as well as progression-free survival (PFS). PD-1 and CTLA-4 are immunological checkpoints [62], with CTLA-4 antibodies being the first FDA-approved ICIs for human usage.

1) PD-1 and PD-L1

Clinical immunotherapy with PD-1/PD-L1 antibodies is a well-researched and popular treatment. T cells, B cells, dendritic cells, natural killer (NK) cells, and tumor-infiltrating lymphocytes (TILs) are among the immune cells that express PD-1 [63]. PD-L1 and PD-L2 are the two ligands for PD-1. PD-L1 is expressed more frequently than PD-L2 in both malignant and healthy cells [64]. Immunological tolerance requires PD-1 in a functioning immune system. The interaction between PD-1 and PD-L1 can prevent the production of cytokines and the proliferation of lymphocytes in the tumor microenvironment (TME). Tumor-specific T cells are killed as a result of cytotoxic T lymphocyte (CTL) activity [65–67] [68]. According to earlier studies, a sizable portion of TNBC patients express both PD-L1 and PD-1, and combination therapy with chemotherapy and PD-1/PD-L1 inhibitors is more effective than single-dose ICIs.[69]. Pembrolizumab plus chemotherapy greatly increased the PFS of patients with PD-L1-positive tumors in clinical trials (Impassion130), whereas nab-paclitaxel plus atezolizumab together had good PFS and safety profile outcomes [70]. Furthermore, the same patient cohort was used in the Impassion131 study to investigate the combination of atezolizumab and paclitaxel. If the PFS results were good and an Intent-to-Treat (ITT) strategy was used, then only then would the overall survival (OS) be examined. Interestingly, the PD-L1-positive population showed no evidence of increased PFS (6.0 versus HR 0.82 over 5.7 months, p = 0.20). Atezolizumab should only be administered in conjunction with nab-paclitaxel as a result. Because breast cancer is resistant to immune checkpoint inhibitors (ICIs), PD-1/PD-L1 inhibitors have limited single-agent activity in triple negative breast cancer (TNBC). [71]



Effects of inhibitors of PD-1 and PD-L1. T-cell mortality brought on by the combination of PD-1 and PD-L1 results in tumor cell invasion. T-cell tumor-killing efficacy is increased when PD-1 or PD-L1 inhibition is applied, as this increases proliferation of T cells, activation, and cytokine release.

2.CTLA- 4

According to the most recent studies, CTLA-4 is elevated in tumor patients, indicating its importance as an immune evasion mediator. As a negative regulator, it is mostly expressed on T cells [73], and when it interacts with its ligand, CD80/CD86, it reduces the T cell responses that are elicited when CD28 is bound to [62]. According to reports, CTLA-4 is expressed by TNBC tumor cells. To inhibit CTLA-4 and extend PFS and OS, anti-CTLA-4 monoclonal antibodies can be utilized [74]. Both drugs have shown promise in the treatment of different cancers, and researchers anticipate that TNBC patients will benefit from them in a similar way.[75]. However, it is important to note that more research is need to determine the safety of CTLA-4 inhibitors., so use them with caution. Combining surgery or chemotherapeutic treatment with immune checkpoint medication therapy can improve cure rates for TNBC patients. We are optimistic about their future prospects.

3) Antibody-Drug Combination (ADC)

ADCs offer a potentially effective avenue for cancer treatment because, in comparison to conventional chemotherapy, they can specifically target cancer cells with less damage to healthy cells and fewer side effects.[76]. ADCs' antibodies are made to attach to particular proteins on the surface of cancer cells so that they can directly deliver a lethal payload to them. This customized approach is particularly critical for TNBC, as it is well recognized to be highly heterogeneous and challenging to treat conventionally. ADCs therefore provide a novel therapy option for this aggressive kind of breast cancer.

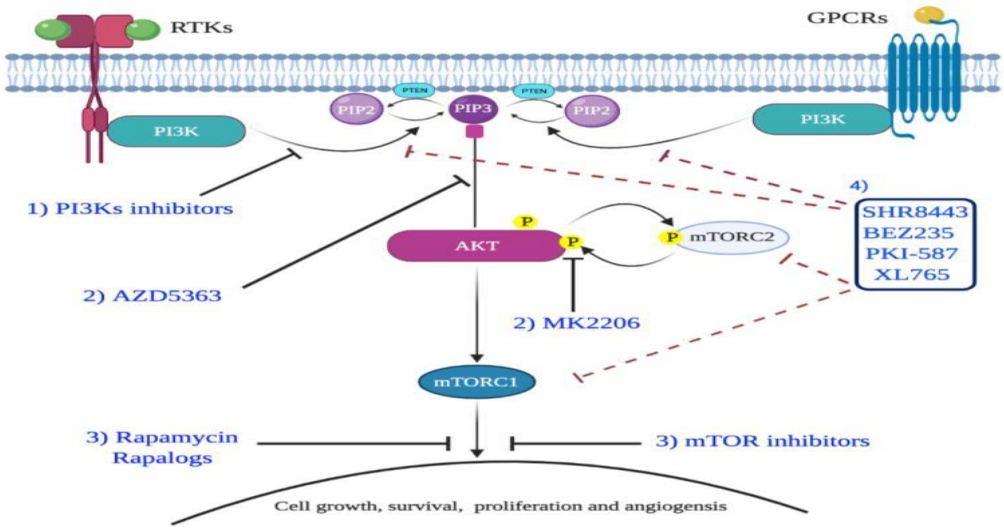
The anticancer drug SN-38 [77], a metabolic product of irinotecan (topoisomerase I inhibitor), is coupled to antitrophoblast surface antigen 2 (Trop-2) in sacituzumab govitecan (SG), a novel ADC [78, 79]. Many cancer types, including those of the colon, prostate, breast, lung, and pancreas, have increased expression of trop-2. Since Trop-2 is overexpressed in a lot of epithelial cancers, it could be used as a therapeutic target [79–81]. In one research, ADC treatment resulted in a PFS of 5.5 months on average and a 33% OS rate. The phase III ASCENT trial sought to evaluate the safety and effectiveness of SG vs traditional chemotherapy in the treatment of relapsed or resistant triple negative breast cancer.. As per standard of care, on days one and eight of each 21-day cycle, patients were randomly assigned to receive either 10 mg/kg body weight of SG or a single chemotherapeutic medication. In comparison to patients receiving chemotherapy, the study indicated that those treated with SG had significantly greater median progression-free survival (PFS) (4.8 months vs 1.7 months) and overall survival (OS) (11.8 months, 95% CI: 10.5-13.8 months versus 6.9 months, 95% CI: 5.9-7.7).[81-83]. These results imply that SG is more efficient than chemotherapy. Both groups reported the same adverse effects, including loss of hair, neutropenia, diarrhea, nausea, tiredness, and anemia [84]. The FDA gave expedited clearance to SG for treating TNBC patients with metastases who had undergone at least two previous therapy.

An alternative anti-drug conjugate (ADC) called ladiratuzumab combines monoclonal antibodies directed against the transmembrane protein LIV-1, which is a metalloprotease and zinc transporter. Although expressed in less healthy areas, this protein is found in nearly 90% of cases of breast cancer. The microtubule inhibitor MMAE is also present in ladiratuzumab. The safety and effectiveness of a combination of

ladiratuzumab vedotin, pembrolizumab, and the chemotherapeutic drug eribulin for the treatment of advanced HER2-low TNBC were assessed in a phase II clinical trial. Initial findings showed that the ladiratuzumab vedotin combination group had an overall response rate (ORR) of 58.3%, with 12 patients (30%) achieving a full or partial response, as opposed to an ORR of 25% and 4 patients (20%).In the eribulin monotherapy group, patients achieved complete or partial responses. In addition, the combination of ladiratuzumab with vedotin showed a longer response time. This combination of ladiratuzumab vedotin, pembrolizumab, and eribulin appears to be a potential therapy choice for HER2-low advanced TNBC patients [85].
Trastuzumab deruxtecan (T-Dxd) is a form of ADC that targets HER2. It is a humanized monoclonal antibody derived from trastuzumab's amino acid sequence. This is the first HER2-targeted drug to show effective In HER2-negative individuals, clinical antitumor efficaciousness and tolerable safety.. T-Dxd is FDA-approved for treating HER2-positive Breast cancer with metastases [86]. Breast cancers with low HER2 expression (IHC1+ or IHC2+/FISH-) are currently considered HER2-negative. As a result, some of these cases are handled as TNBC [87].

4) The PI3K/AKT/mTOR pathway

The RTK family of enzyme-linked receptors consists of the extracellular ligand binding area, a single transmembrane helix, a paramembrane regulatory region, and a protein tyrosine kinase structural domain. There are 58 different receptors, including as AXL, VEGFR, EGFR, FGFR, and IGF-1R [88]. RTK activates multiple downstream pathways after ligand contact and receptor dimerization, including the Pathways that activate transcriptional proteins include Janus kinase/signal transducer sub, RTK/Ras/MAPK, PI3K/AKT/mTOR, and others.[88, 89]. The PI3K/AKT/mTOR pathway is essential for many cellular functions, such as metabolism, proliferation, migration, and survival. It also plays a major role in TNBC cell survival and chemoresistance. Roughly 50% of TNBCs have abnormalities in this route.[90]. The 4,5-phosphatidylinositol (PIP2) is phosphorylated to 3,4,5-phosphatidylinositol (PIP3) by PI3K, which is activated by RTK. This pathway is frequently dysregulated in TNBC [91]. PIP3 then attaches itself on AKT, phosphorylating serine and threonine to make AKT fully active.[92-94].Additional modulators of this cellular route are PTEN, which obstructs PI3K signaling phosphatase and can restrict tumor development by converting PIP3 to PIP2 [95].TNBC cells have been shown to exhibit abnormalities in the PI3K/PTEN/AKT pathway, including activating changes in PIK3CA and AKT1, loss of PTEN, and mTOR activation.[96-99] in more than 25% of individuals with TNBC, suggesting that targeting this route is a viable treatment for TNBC.[96]. The efficacy and safety of using the mTOR inhibitor everolimus in conjunction with the chemotherapeutic drug carboplatin to treat advanced triple negative breast cancer were evaluated in a phase II clinical trial. The findings revealed that the combination treatment improved PFS in individuals, while adverse effects were rather common [100]. An additional phase II clinical investigation was done to assess the efficacy and safety of combining the chemotherapeutic medication paclitaxel and the AKT blocker TNBC is treated with ipatasertib.



PI3K-AKT-mTOR- Schematic-diagram [85]

Targeted therapy

Targeted therapy for TNBC is safer for healthy cells than chemotherapy. Several supressors have been investigated as potential treatments for TNBC, including EGFR, PARP, VEGF, PIK3, MEK, and AR inhibitors [101].

1.Antiandrogen Therapy

According to a study, some TNBC subtypes have downstream consequences including androgen receptor activation similar to LAR tumours. [102]. In contrast to its function in ER+ breast cancers, this fraction of TNBC stimulates the growth of tumour cells via means of androgen receptor hormone signalling.[103]. According to a study, over 35% of TNBC express the androgen receptor (AR), which raises the possibility of using it as a therapeutic target. [104]. Preclinical research indicates that combining PI3K pathway inhibitors with AR antagonists might significantly suppress the development and survival of LAR cell lines; AR-positive breast cancer patients have a higher frequency of PIK3CA activating mutations than AR-negative persons. [105]. Alternatively, a another study found that phosphorylation of CDK4/6 is more important for AR-positive TNBC. The safety and effectiveness of palbociclib (a CDK4/6 inhibitor) and bicalutamide were studied in a phase I/II trial conducted in AR-positive TNBC [106]. With a 6 month PFS rate of 33%, the clinical trial achieved its main objective.[107] . An further experiment called GeparNuevo evaluates the impact of three treatment arms on patients' disease-free survival (DFS) in cases of early HER2-positive breast cancer.. In comparison to normal targeted therapy alone, the results showed that adding ribociclib to standard targeted treatment significantly enhanced DFS although adding chemotherapy had no further therapeutic benefits. Ribociclib, a CDK4/6 inhibitor, may improve treatment outcomes regarding early-stage HER2-positive breast cancer[108].

2.The MAPK pathway

Small GTPases called N-Ras, M-Ras, K-Ras, and H-Ras are first triggered by external cues like ligand activation of RTKs.[109]. Ras signals enhance cell survival and proliferation by travelling to the nucleus through downstream effectors like Raf, MEK, and ERK.[110]. TNBC cell lines' proliferation can be inhibited by the MEK inhibitor, a crucial part of the Ras/MAPK pathway. Considerable enhancement in PFS in contrast to placebo. This suggests that MAPK pathway blockers could be effective therapy alternative. Although the clinical effects of combination therapies are still unknown, several studies indicate that they may be more effective than using MEK inhibitors alone.

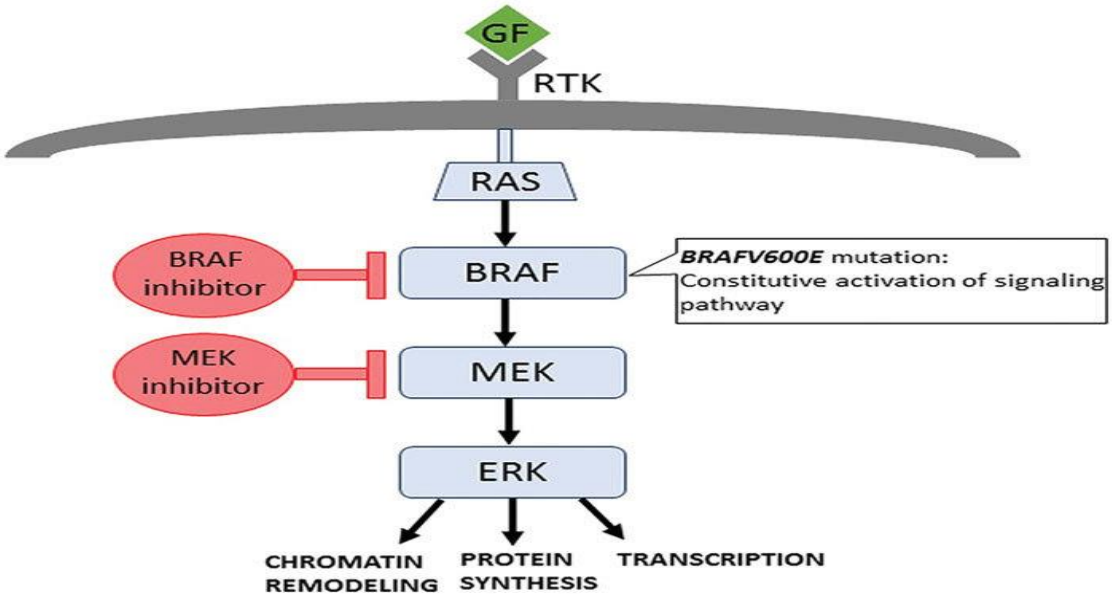


Diagram showing the receptor tyrosine kinase (RTK) and growth factor (GF) in the mitogen-activated protein kinase (MAPK) pathway. [111]

3.PARP inhibitors

Mutations in the breast cancer susceptibility gene (BRCA) are found in about 20% of TNBC patients, making it one of the most frequent genetic changes seen in this population [112]. BRCA1 and BRCA2 may fix fractures in healthy cells, and double-strand breaks in DNA are common during the carcinogenesis process. [113, 114]. Over 15% of TNBC patients have BRCA1 or BRCA2 mutations, and there are both clinical and pathological similarities between individuals with BRCA2 mutations and TNBC patients [115, 116].PARP, a DNA repair enzyme, performs a crucial role in ensuring normal DNA replication and repairing breaks in single-stranded DNA, especially in the presence of BRCA mutations. Therefore, targeting PARP is a possible option. Damage to PARP might delay DNA repair and increase cell vulnerability to DNA breaks [117]. By blocking DNA repair recombination via polyADP ribosylation or homologs, PARP inhibitors produce cytotoxicity.[118]. Olaparib, niraparib, fuzoparib, and pamiparib are the four PARP inhibitors that are currently authorised for commercialization. [119].Breast cancer can be effectively treated with olaparib alone or in combination with chemotherapy, immunotherapy, and radiation therapy.

Gene Therapy for TNBC

Gene therapy is one of the most thoroughly studied treatment techniques in recent years. RNA-based therapeutics are a novel strategy to cancer treatment that can target some of the primary tumor processes that resulted in unfavorable patient outcomes.[120]. Long noncoding RNA as well as miRNA are the two main kinds of noncoding RNAs under investigation. miRNA attaches may deteriorate or obstruct translation by binding to the untranslated region at the 3' end of mRNA.[121]. Despite their crucial involvement in biological processes such as regulating gene expression, cell proliferation, and death at the transcription, posttranscriptional, and posttranslational modification stages, LncRNAs are misexpressed in TNBC.[122]. As a result, while lncRNAs offer promise as prospective goal for the management of TNBC, they must defeat current constraints. RNA disruption is a gene-targeting technique that interferes with RNA molecules to specifically prevent the expression of particular genes. RNA interference technology is being used in some TNBC therapeutic research to target genes like FOXC1, CXCR4, and CLDN3 that are linked to cancer cell growth and metastasis. The transcription factor FOXC1 has been associated with the proliferation and metastasis of cancer cells [123]; Cancer cell invasion and metastasis have been linked to the chemokine receptor CXCR4.[124]; moreover, the cell adhesion protein CLDN3 has been connected to the spread of cancer cells [125]. Therapeutic effects can be achieved by efficiently inhibiting cancer cell proliferation and metastasis through the use of RNA interference technology to target these genes[126].

Conclusion

TNBC generally has the worst overall prognosis, the highest rate of recurrence, and the highest aggressiveness of all the breast cancer subtypes. Despite continuous investigations Over the past few decades, existing treatments have proven unable to address these issues. Nonetheless, significant progress has been made in adjuvant treatment for TNBC, which has somewhat improved patient prognosis. Moreover, immunotherapy is essential to the treatment of TNBC because of its distinct features. The FDA's recent approval of CTLA-4 antibody usage has given TNBC treatment a new direction due to advancements in ICIs. Additionally, ADCs have started TNBC clinical trials, with the FDA having authorized sacituzumab govitecan. Additionally promising in terms of enhancing the prognosis for TNBC is the combination of immunotherapy and other treatments. There is optimism for improving patient outcomes with additional therapy options and a deeper understanding of TNBC through ongoing trials. The advancement of nanotechnology has garnered significant interest from scholars; nevertheless, in order for nanotechnology to continue to play a bigger role in the future, its inadequacies must also be continuously addressed.

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