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Triple-Negative Breast Cancer (TNBC) Management: A Review of Conventional and Contemporary Treatment Strategies

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Abstract

Triple-negative breast cancer (TNBC), a heterogenous subtype of breast cancer, is estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, human epidermal growth factor receptor-2 (HER2)-negative and is the second leading cause of cancer-associated mortality in women. The poor prognosis and an aggressive clinical course of TNBC warrants further research for therapeutic options. The current treatment alternatives, along with the potential therapeutic targets for TNBC have been enlisted here. Therapeutic benefits of AMPK modulation, androgen receptor (AR) antagonists, epi-drugs, immunotherapy, mTOR inhibition, PARP inhibition, platinum-based chemotherapy and various such modalities have been discussed. A reduction in cancer growth through AMPK activation by some drugs has directed research towards developing AMPK agonists and antagonists. mTOR suppression via AMPK pathway activation has shown to result in loss of tumor cell proliferation and glucose synthesis and thus, provides a beneficial outcome. Since many TNBC tumors express androgen receptors (AR), many agents which antagonize AR have been implicated in the treatment of TNBC. Regulation of epigenetic proteins by epi-drugs has shown to activate the apoptosis pathway, suppress the survival pathway and has been investigated. A detailed research on immunotherapy utilization in TNBC has emphasized its part in constraining tumor cell activity. Also, PARP inhibition has been associated with prolonged survival, especially in BRCA1/2 germline mutations and several combination regimens of PARP inhibitors with other drugs have been studied. Promising results of platinum-based neoadjuvant chemotherapy have been reported to prevent recurrences, compared to the standard scheduled therapy. This review aims to summarize existing as well as the feasible therapeutic courses of action for TNBC.

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INTRODUCTION

Breast cancer is the leading type of invasive cancer in women, accounting for an estimated 30% of all cancers, and the second leading cause of cancer-associated mortality in women after lung cancer. Worldwide, 2,261,419 new breast cancer cases were reported in 2020 and resulted in 684,996 deaths. Of all the breast cancer subtypes, triple-negative breast cancer (TNBC) accounts for 15-20% of cases, and is widespread in women under the age of 40 years [1]. It is defined as the subtype of breast cancer that does not have any of the receptors com-

monly found in breast cancer. TNBC cells are not positive for estrogen receptors (ER), progesterone receptors (PR), and human-epidermal growth factor receptor-2 (HER2) amplification. It is characterized by a poor prognosis, an aggressive clinical course, and a high metastatic potential with the five-year survival rate being lower than that of other breast cancer types. The lack of expression of these molecular markers and the inherent heterogeneity, leaves cytotoxic chemotherapy, surgery, and radiation therapies as the only suitable treatment options for TNBC. Burstein et al. proposed four molecular subtypes of TNBC, which included luminal androgen-receptor (LAR), mesenchymal (MES), basal-like immune-activated (BLIA) and basal-like immunosuppressed (BLIS) types [2]. More recently, Liu et al. gave another four subtypes classification, dividing it into luminal-androgen receptor (LAR), mesenchymal-like (MES), immunomodulatory (IM) and basal-like immunosuppressed (BLIS) types. Differences in each of these subtypes are due to different genetic mutations. A miscellany of results of these studies suggested mainly four subtypes, luminal-androgen receptor (LAR), immunemodulatory (IM), mesenchymal-like (MES), and basal-like (BL) types. LAR subtype is denoted by enrichment of steroid biosynthesis, porphyrin metabolism, androgen/estrogen metabolism, and PPAR signaling. An apocrine subtype has been identified under LAR [3]. This subtype shows an unfavorable prognosis and its immunochemistry (IHC) marker is the androgen receptor (AR). Mesenchymal-like (MS) subtype, with a fairly intermediate prognosis, is characterized by an augmented epithelial-mesenchymal transition (EMT) and stem cell-like feature. The MS subtype markers include claudin and E-cadherin. It shows discohesive tumor cell proliferation and metaplastic features [4]. Immunomodulatory (IM) subtype, having medullary histology has a favorable prognosis and shows genetic alteration in immune cell signaling, cytokine signaling, antigen presentation, and immune signal transduction. The basal-like (BL) subtype shows cell cycle- and proliferation-related alterations, and alterations of DNA damage. CK-5/6 and EGFR are the markers for this subtype and implicates an unfavorable prognosis [3].

Conventional Strategies

6-MP and 5-AzaC Combination

There is a chance of a minimal residual disease (MRD) after chemotherapy and surgery because of some resistant cells which switch between quiescence and proliferation and hence, the likelihood of relapse and the capacity to metastasize increases. In a recent study, inhibition of resistant TNBC cells with low dose 6- mercapto-purine and 5-azacytidine was shown. Low-dose, 1uM 6-MP is used, and 5-AzaC to complement the actions of 6-MP (both ribonucleoside analogs). This combination also minimizes the inflammation commonly associated with cancers. A significant cell growth inhibition was observed after weeks of treatment and resistant fast-growing colonies did not occur. 5-AzaC alone did not inhibit growth after several weeks, but a low dose (1uM) 5-AzaC enhances doxorubicin sensitivity. Also, when co-administered with 6-MP, significantly faster growth inhibition was reported, higher than that with 6-MP alone and quiescent cells began to proliferate after 6-MP was withdrawn. The cells remaining after this treatment were sensitive to the conventional chemotherapy [5] (Figure 1).

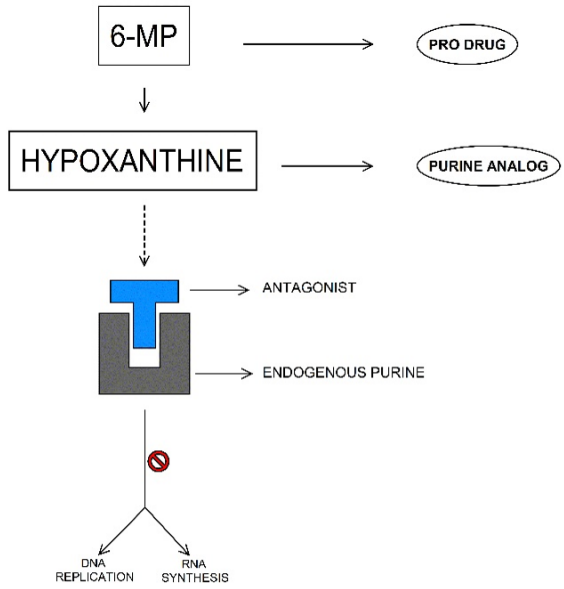

Figure 1: Hypoxanthine, a Product of 6-MP Activation, Acts as an Antagonist to Endogenous Purine Receptors; This Hinders DNA Replication and RNA Synthesis in Tumor Cells

Anti-Angiogenic Therapy

A study constructed to find out if a low-dose anti-angiogenic agent acts synergistically with a PD-1 inhibitor (immune-checkpoint inhibitor), demonstrated that VEGFR2 blockade sensitizes the cells to PD-1, by upregulation of PD-1 on tumor cells. It causes immune cell infiltration, increases the secretion of OPN (osteopontin) via CD8+ T-cells, and increases TGF-b production of tumor cells. The combination proved to be tolerable and efficacious in TNBC; however, both showed limited activity when used as single agents. Anti-angiogenic agents work by normalizing tumor vasculature and low-

ering immunosuppression. Low-dose (10 mg/kg) anti-VEGFR, DC101 was tested and it was found that low-dose seemed to respond better in improving the anti-tumoral activity of PD-1 inhibitor as compared to high dose [6]. The GeparQuinto study reported the response and prognosis results of the use of bevacizumab in the neoadjuvant treatment of TNBC. BRCA1/2 mutant TNBC patients showed a better pCR. The addition of bevacizumab to the standard chemotherapy increased the pCR in BRCA1/2 mutation cases because of the synergistic action which is produced when an anti-angiogenic i.e. bevacizumab induces hypoxia in cancerous cells, which in turn leads to down-regulation of DNA repair pathways [7].

CDK Inhibition

A trial studied trilaciclib, a CDK4/6 inhibitor, which arrests immune cells and hematopoietic stem cells in the G1 phase of the cell cycle, and consequently protects the cells from the cytotoxic effects of chemotherapy by minimizing myelosuppression and optimizing chemotherapy. The results reported no significant myelo-protection but was shown to be beneficial for overall survival and an improved anti-tumour activity when co-administered with carboplatin and gemcitabine [8]. Dinaciclib is another CDK inhibitor, which downregulates MYC and shows a synergistic effect in combination with PARP inhibitors [9].

Immunotherapy

A preclinical trial in patient-derived xenografts assessed the effectiveness of simultaneous targeting of HER family. Also, EGFR has been known to be overexpressed in TNBC, making it a possible target for therapy. Pan-HER, a mixture of 6 monoclonal antibodies, is directed against several HER/EGFR members like EGFR, HER1, HER2, HER3, etc. These (particularly EGFR and HER3) are downregulated in TNBC tumors and the associated signaling pathways are blocked. This mAb combination prevents tumor recurrence and also, resistance. A more pronounced response was reported in TNBC patients exhibiting highly active HER expression. This trial in patient-derived xenografts (PDX) showed pan-HER to produce complete tumor regression in some of the models tested [10]. A study, IMpassion 130, assessed the efficacy and safety of adding atezolizumab, an anti-PDL1 antibody to nab-paclitaxel standard chemotherapy as the first-line treatment for unresectable, locally advanced, or metastatic breast cancer. The results of this study reported no significant difference in the overall survival (OS) between atezolizumab and placebo groups, but a remarkable benefit in overall survival in patients with PD-L1 positive tumor was found [11]. Another research investigated durvalumab in addition to an anthracycline taxane-based neoadjuvant therapy in early triple-negative breast cancer (GeparNuevo study) and reported a higher rate of pathologic complete remission (pCR) in patients treated with durvalumab alone for 2 weeks before the start of therapy. A significantly increased pCR was demonstrated with higher stromal TILs levels in both durvalumab and placebo-controlled arms. Durvalumab has been known to modulate the tumor microenvironment by stimulating the lymphocytes to migrate from the stroma into the tumor cell and it has been observed that the overall higher expression of PD-L1 is associated with a higher response, but that does not predict durvalumab response [12]. CTLA-4 inhibitors, ipilimumab and tremelimumab, which are currently under trial, can be promising agents for TNBC expressing MAGE-A antigen (an aggressive sub-group). For TNBC that expresses MAGE, the melanoma-associated antigen vaccine would be a potential therapeutic target. Genetically modified T-cells, expressing a chimeric-antibody receptor (CAR) specific for mesothelin (mesoCAR T cells) are upregulated in TNBC and hence, it could be a target in the TNBC cure. Passive immunotherapies such as chimeric antigen receptor (CAR) T cell therapy, which includes genetically engineered T-cells could be used in patients with an intact immune system. Oncolytic immunotherapy (chimeric parapoxvirus CF189)- Talimogenelaherparepvec (T-Vec) is approved by the US-FDA for cancer treatment and has shown minimal toxicity to healthy cells. Therapeutic vaccines for cancer act by causing the immune system to attack the cancerous cells and some of the vaccines studied include the DR5 DNA vaccine: TRAIL-R2/DR5 is overexpressed in many solid tumors and the DR5 DNA vaccine has shown to cause apoptosis and induction of IF-y secreting T-cells. Combined vaccinations such as IGF-1R/HER-1 antibodies increase the efficacy of HER-1 targeted immunotherapy such as cetuximab. TNBC is a cancer-testis antigen (CTA) rich cancer; so CTA-based tumor vaccines might turn out to be an option. Examples include NY-ESO-1, maybe in combination with MAGE-A10, anti-SP-17 antibodies, and MAGE-A/B vaccines [1]. JAVELIN Solid Tumor study assessed the safety and efficacy of avelumab in patients with locally advanced or metastatic breast cancer, including TNBC. It is an anti-PD-L1 IgG1 monoclonal antibody, which acts as an immune checkpoint inhibitor and restores the immune surveillance in tumor cells. Higher levels of PD-L1 have been associated with an increased probability of clinical response in metastatic breast can-

cer patients. Avelumab demonstrated modest antitumor activity with a good safety profile and the frequency of immune cell subsets did not decrease following avelumab treatment [13].

Natural Analogs

A recent research reported capsanthin, a carotenoid derivative, to have alleged antitumor and antioxidant effects. It has been shown to inhibit the activity of a polycomb group EZH2 protein and mRNA, which epigenetically regulates p21 and cyclin A (checkpoints). Thus, dysregulation of the cell cycle due to overexpression of EZH2 is prevented and p21 levels are upregulated, which results in cell-cycle arrest at the G1/S phase, and prevention of tumor proliferation. It has also been found to act synergistically with erlotinib (tyrosine kinase inhibitor), and increase its sensitivity in chemotherapy-resistant cells [14]. RL71, a second-generation curcumin analog, triggers uncontrolled autophagic cell death, exhibiting effective anticancer activity in TNBC cells. Besides, it also raises the release of Ca2+ from the endoplasmic reticulum into the cytosol by repressing sarco/endoplasmic reticulum calcium-ATPase 2 (SERCA2) activity, causing autophagy via several mechanisms [15]. Another research has shown a significant effect of berberine (BBR), a Chinese alkaloid, on tumor outgrowth and metastasis. Evidence suggests that inflammation is closely associated with the initiation and progression of tumor and metastasis as well. So, modulation of inflammation seems to be a good anti-tumor target. BBR has been used for many purposes, of which anti-inflammation is a significant one. Its anti-tumor activity mechanism has been found to be due to varied mechanisms like autophagy, apoptosis, RO species generation, cell cycle arrest, and also, regulation of NLRP3 inflammasome pathway in macrophages. In vitro studies suggested that it decreased the number of colonies and their cell migration as well, hence, lowering the metastatic potential. Other than that, excessive secretion of cytokines by cancerous cells was also reduced and hence changes the tumor microenvironment. IL-6 and TNF-a levels are also suppressed by the action of BBR [16]. However, another study showed that the tumor lysis through this mechanism was inadequate and implicated the participation of another mechanism that leads to excessive autophagy, i.e. release of calcium from ER can induce autophagy, depending upon Ca++/calmodulin dependent kinase-B-dependent activation of AMPK. This leads to inhibition of mTOR [17].

PARP Inhibitors

Talazoparib exhibits improved global health status and quality of life in TNBC patients. Veliparib is under investigation and it has demonstrated good anti-tumor activity in TNBC patients when used in a combination with temozolomide. Combination therapies with PARPi and Wee1 kinase inhibitors in TNBC cells with either BRCA1 mutations or high levels of cyclin E result in synergistic cell death due to induction of replicative stress and down-regulation of DNA repair. BRCA1/2 germline mutations are correlated with prolonged survival in TNBC since the tumors with these mutations are more susceptible to therapies, such as platinum, alkylating agents, anthracyclines, or PARP inhibitors. Moreover, PARP inhibition also augments stress on the replication forks. The BRCA1/2 breast cancer mutation carriers with elevated cyclin E levels have ascertained a higher recurrence rate than those with low-cyclin E levels. TNBC cell lines with high low-molecular weight cyclin E (LMWE) expression were more susceptible to PARPi (MK-4827). Combination treatment with PARPi (MK-4827) and Wee 1i (AZD-1775) can synergistically inhibit tumor growth in vivo by inducing apoptosis; and suppress multiple DNA repair pathways causing extensive DNA damage, leading to cell death [18]. The randomized, phase 3 OlympiAD trial demonstrated olaparib to have good activity in luminal-like and TNBC subtypes with BRCA mutations [19]. PARP inhibitors have not been approved for TNBC treatment, with BRCA mutation. However, many studies are being conducted to test their therapeutic efficacy in TNBC treatment. BRCA1 mutation is thought to be a predisposing factor for TNBC. In a study, olaparib has shown a better progression-free survival than the standard chemotherapy regimens, which consisted of capecitabine [20]. A phase III study has compared iniparib with a combination of gemcitabine and carboplatin (GCI) versus gemcitabine and carboplatin without iniparib (GC), where the former was found to be efficacious in preventing visceral metastasis, but it depended on the previous chemotherapy received. Iniparib has been found to act via Nrf-2 mediated antioxidant response. The benefit was GCI combination was shown in second-/third-line patients and further study is warranted [21].

Platinum-Based Chemotherapy

Neoadjuvant therapy comprising a platinum agent has demonstrated its benefits if residual disease at the time of surgery persists. Studies have reported dose-dense chemotherapy to be effective in preventing recurrences as opposed to standard scheduled therapy. For advanced disease, carboplatin has shown a better toxicity profile and efficacy as compared to docetaxel and research has shown platinum agents to be effective in both metastatic and neoad-

juvant settings [19]. A randomized and open-label phase II trial reported the efficacy of lobaplatin in TNBC. Lobaplatin is associated with a strong anti-cancer activity, low toxicity, and higher solubility and stability in water. The overall response rate was improved with the addition of lobaplatin, showing a better pCR rate than docetaxel and epirubicin alone. The clinical response is achieved at the cost of increased adverse effects when lobaplatin is combined with the neoadjuvant therapy of docetaxel and epirubicin [22]. In patients with BRCA1/2 mutations, carboplatin has shown better progression-free survival (PFS) rates, as compared to docetaxel [23]. TBCRC009 is a multicenter phase II clinical trial that studies platinum monotherapy along with biomarker assessment in metastatic TNBC. Nearly 80% of breast cancers arising in BRCA1 mutation carriers are TNBCs, and these tumors are characterized by a defect in DNA double-strand break-repair, which makes them especially susceptible to DNA cross-linking agents, including platinum analogs. High pathologic complete response (pCR) rates have been identified among BRCA1 carriers treated with cisplatin in the preoperative setting, and high response rates (RRs) were also observed among a small cohort of BRCA1 carriers treated with cisplatin in the metastatic setting [24].

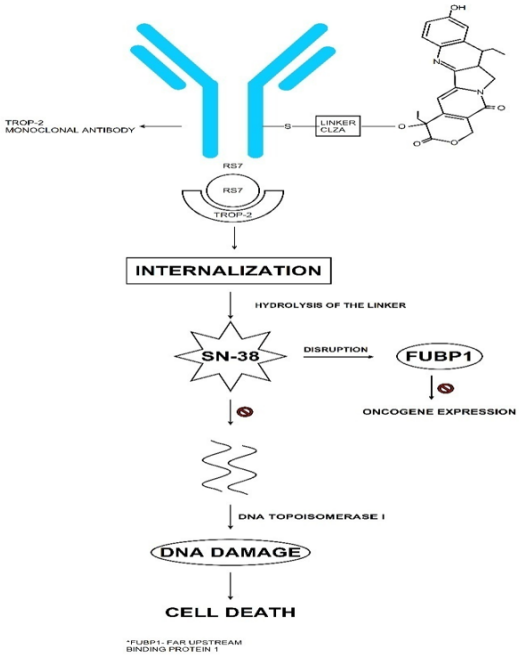

Figure 2: Sacituzu Mab Govitecan is a Trop-2 Monoclonal Antibody which Releases the Active Metabolite SN-38. SN-38 Inhibits Oncogene Expression via Disruption of FUBP-1; also Results in DNA Damage Through DNA Topoisomerase I Inhibition

Contemporary Strategies

AB-Drug Conjugate

Trop-2 over expression is indicative of poor prognosis in cancers and hence, targeting Trop-2 would be an effective therapeutic strategy. Sacituzumab govitecan (IMMU-132) is an anti-trop-2 antibody carrier that carries SN- 38, which is an active metabolite of a TP-I inhibitor, irinotecan. Evidence has shown that it provides higher drug delivery to tumor cells and a better therapeutic index in pretreated metastatic TNBC patients and also demonstrated ADCC in in-vitro models. This antibody-drug conjugate showed favourable anti-tumor activity and a manageable safety profile [25]. (Figure 2)

AMPK Pathway

Research studies have established the therapeutic benefits of AMPK agonists and antagonists in certain cancer types. An augmented resistance to death in several cells has been shown in response to AMPK activation. A decrease in cancer growth by AMPK activation, induced by drugs, has been known. AICAR lowers MTDH expression by stimulating GSK3β and SIRT1, via suppressing c-Myc in TNBC cells. This action of AICAR corresponds to AMPK activation, which promotes growth arrest, anti-proliferative effects and inhibits migration of TNBC cells. A selective serotonin reuptake inhibitor (SSRI), fluoxetine, effectually inhibits tumor growth of TNBC via promoting apoptosis and autophagy related with eEF2K suppression and AMPK-mTOR-ULK activation signalling pathway. These results directed the conclusion that AMPK may be a novel anti-TNBC target [15] (Figure 3).

AR Antagonists

Androgen receptor (AR) is a steroid hormone receptor, manifested in many subtypes of breast cancer. Studies have found a significant relevance of AR in breast carcinomas. A lot of PI3K mutations have been observed in AR-positive TNBC, so a combination of PI3K/mTOR inhibitors with AR antagonists has demonstrated a synergistic activity in preclinical models. Hence, palbociclib in combination with taselisib/pictilisib for PIK3CA mutant ER (-) breast cancer is under trial [9].

The growth of tumor cells expressing AR is stimulated by AR signaling pathway; hence blocking the same would be an effective strategy in AR expressing TNBC. Bicalutamide and abiraterone acetate have shown an anti-tumor activity in clinical trials. Enzalutamide is another AR antagonist studied [26]. As AR is expressed in the LAR subtype, another AR antagonist, flutamide, was studied for its efficacy in tumors expressing apocrine histology [23] (Figure 4).

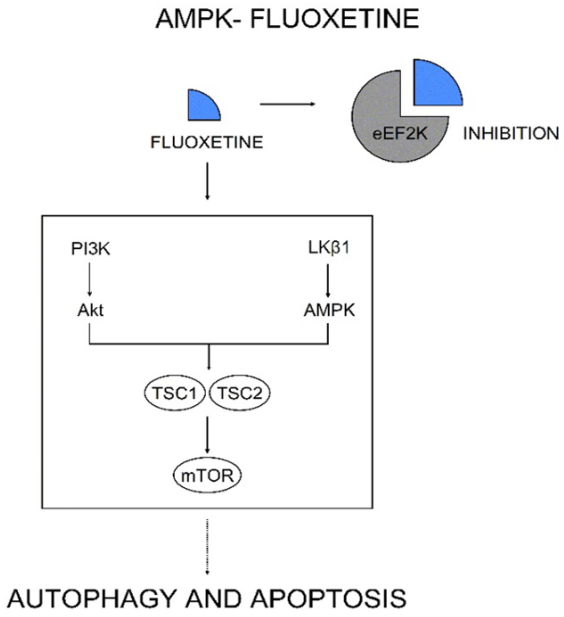

Figure 3: Fluoxetine has been Known to Cause Autophagy and Apoptosis through EF2K Suppression and AMPK-mTOR Activation

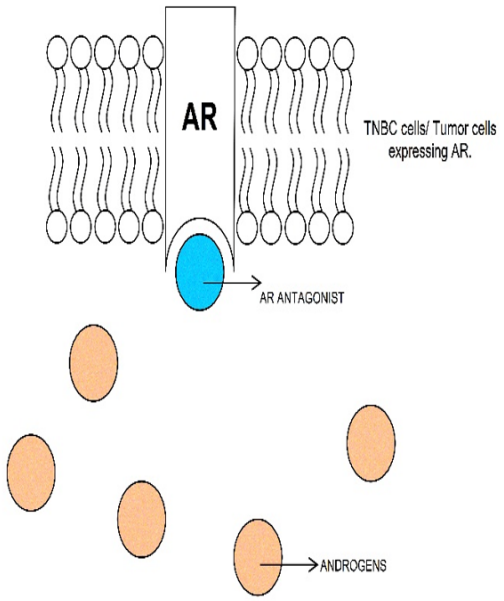

Figure 4: Some of the TNBC Cells Expressing Androgen Receptors are Expected to Respond to AR Antagonists such as Bicalutamide

BET Inhibitors

BET (Bromodomain and Extra terminal) inhibitors, a novel family of compounds being explored, are showing promising results for the treatment of TNBC. They modify the expression of various oncogenic genes via the inhibition of bromodomain-containing proteins [27]. In in-silico and preclinical trials, BET inhibitors show an antitumor effect in TNBC, which is synergized when combined with chemotherapeutic agents [28].

Beta-Blockers

A research has retrospectively reviewed breast cancer patients, including TNBC, on neoadjuvant chemotherapy i.e. anthracycline and taxane-based chemotherapy, who were on beta-blockers (majority-metoprolol, others-atenolol). It is evident that TNBC patients tend to be obese and have some kind of metabolic dysregulation and as we know, the sympathetic nervous system is correlated with adrenergic signaling and hypothalamic-pituitary-adrenal axis (HPA) with glucocorticoid signaling. These pathways lead to tumor growth by means such as angiogenesis. Hence, adrenergic suppression may turn out to be of some benefit. The study results reported an increased relapse-free survival with the use of beta-blockers along with neoadjuvant chemotherapy [29] (Figure 5).

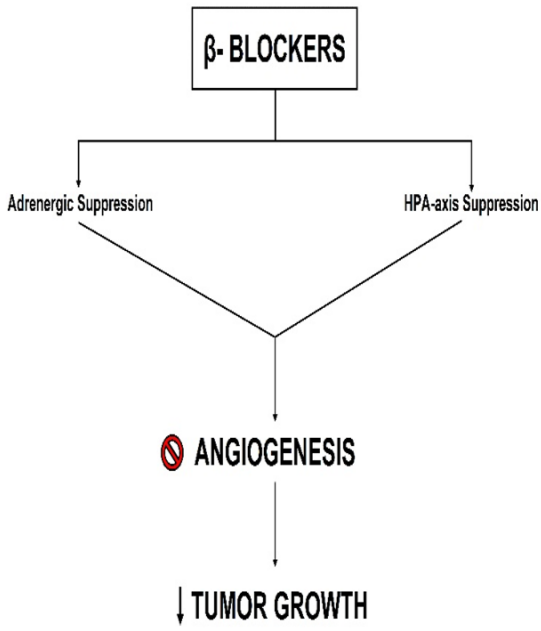

Figure 5: Beta-Blockers Through Adrenergic and HPA-Axis Suppression Inhibit Angiogenesis, Eventually Decreasing Tumour Growth

EPI-Drugs

Epi-drugs modulate epigenetic proteins such as DNA methyltransferase, histone methyltransferase,

demethylases, acetyltransferases, etc., and act on the cancer cells by activating the apoptosis pathway and suppressing the survival pathway. Epi-drugs have been approved for a number of cancers, some of them are undergoing evaluation phases and have been investigated for TNBC treatment. Based on their mechanisms, epi-drugs have been categorized as:

1. Low molecular weight molecules: Different research has shown the efficacy of procainamide in restoring tumor-suppressor expression. Another molecule of this category, disulfiram, inhibits tumor and endothelial cell invasion and has shown its ability in overcoming synergistic resistance with cisplatin in breast cancer cells. Trials have also indicated hydralazine to be effective in solid tumors in combination with a thiazolidinedione and magnesium valproate.

2. Histone methyltransferase (HMT) inhibitors: S-adenosylmethionine analogs, 3-deazaneplanocin A (DZNEP), and arginine methyltransferase inhibitors are some of the HMT inhibitors, capable of preventing carcinogenesis.

3. Demethylase inhibitors: GSK-J4 has been shown to modulate the pro-inflammatory response of macrophages in xenograft studies. Another demethylase inhibitor, 2-PCPA, has been shown to suppress invasion and metastasis of TNBC cells.

4. Histone acetyltransferase (HAT) inhibitors: Chemical HAT inhibitors include TH1834, which in combination with ionizing radiation strongly induces apoptosis and genomic instability in breast cancer cell lines and other cancer types as well. The effects of another chemical HAT inhibitor, NU9056 on breast cancer cells are currently being investigated.

5. Histone deacetylase (HAD) inhibitors: Panobinostat has been shown to be efficacious when used alone or in combination, and has low toxicity. Entinostat is an oral histone deacetylase inhibitor, which has been shown to be efficacious in ER+ breast cancer in a combination with aromatase inhibitors and also for ER+ breast cancer and TNBC, in a combination with azacytidine; and with trastuzumab for HER2 breast cancer. Resveratrol has shown to be significantly active in inducing premature senescence and inhibiting the epithelial-mesenchymal transition of cancer cells. Other HAD inhibitors include vorinostat, trichostatin A, valproic acid, and sirtinol.

6. Therapies targeting microRNAs: Tumor suppressor miRNAs such as miRNA-127 prodrug mimics, reduce the viability and motility of TNBC cells, making them more sensitive to chemotherapy. Oncogenic miRNAs/oncomiRNA/oncomiR inhibitors include antisense oligonucleotides or antagomiRs, which have been shown to inhibit breast cancer metastasis in mice and primates [30].

ER-b Knockdown

A poor prognosis of TNBC has been made evident in cases of high ER-b expression. When the usual targets are absent in TNBC, the expression of the ER-b gene and protein increases, and an increase in invasion, migration and proliferation of TNBC cells occur due to activation of ER-b. Activation of ER-B also enhances the secretion of IGF2 and upregulates insulin receptors (IR). A marked increase in apoptosis was seen when ER-b was knocked down in TNBC cells. Hence, the co-expression of ER-b and IGF2 was responsible for overall survival reduction in TNBC patients, implying future possibilities of ER-b as a therapeutic target for TNBC [31].

Fluoro-Neplanocin

The anti-proliferative and anti-migration activities of Fluoro-Neplanocin A(NepA) through inhibition of histone H3 methylation in TNBC have been reported in a few studies. Dysregulation in adenosine signaling has found to be related to cancer progression, hence nucleoside analogs may play a beneficial role in management. Neplanocin A(NepA) is an adenosine analog which has been shown to inhibit SAH (s-adenosylhomocysteine hydrolase), an enzyme that catalyzes s-adenosylhomocysteine to L-homocysteine and adenosine so, the inhibition leads to overaccumulation of s-adenosylhomocysteine and lower levels of adenosine. Fluoro-NepA also inhibits histone methylation of cancer cells in TNBC. It suppresses the DOT1L expression on TNBC cells and also inhibits EMT (upregulates E-cadherin and downregulates N-cadherin and vimentin), and therefore, cell invasion and migration are suppressed [18] (Figure 6).

Hippo Pathway/YAP Signaling

The Hippo pathway is a signaling cascade that plays a role in regulating the organ size by modulating cell proliferation, apoptosis, stem cells and hence, limiting the cell size. The primary protein involved in the Hippo signaling, YAP, has been implicated in several human cancers such as gastric cancers and

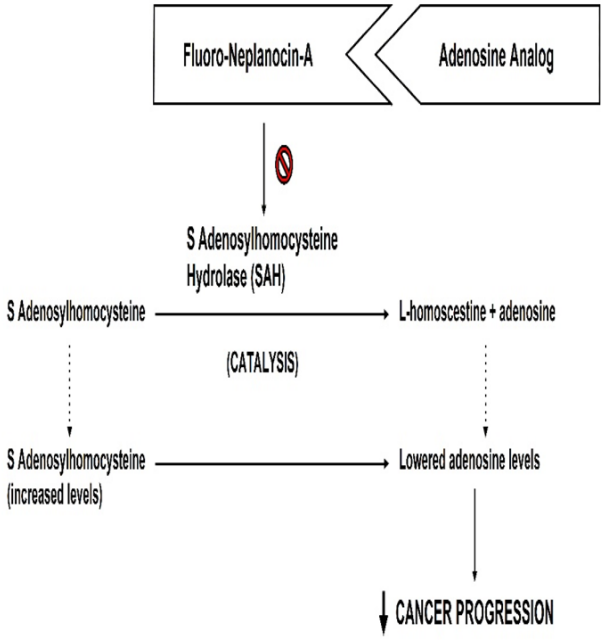

Figure 6: Fluoro-Neplanocin-A, Being an Adenosine Analog, Inhibits the Enzyme SAH. This Results in Accumulation of S-adenosylhomocysteine and Lowered Levels of Adenosine, Causing A Reduction in Cancer Progression

TNBC. YAP has been reported to be involved in modulation of several aspects of TNBC such as cancer invasion, migration, and "stemness". Also, a zinc finger protein member, ZNF213, is shown to be elevated in breast cancer than with normal breast tissues, and its expression has been correlated with a longer relapse-free survival in breast cancers, including TNBC subtypes. Conversely, YAP expression is related to poor survival of TNBC patients. ZNF213 depletion promotes breast cancer cell invasion and migration, and also increases YAP protein level, whereas its overexpression inhibits cancer cell invasion and migration. Nevertheless, the silencing of ZNF213 promotes the YAP target gene expression, including CTGF and CYR61. ZNF213 depletion elevates YAP level, which could further be inhibited by knocking-down YAP. ZNF213 and YAP protein interaction promotes its degradation in TNBC cells. Hence, ZNF213 could possibly be a novel therapeutic strategy for TNBC [32].

IAP Antagonist

A combination of paclitaxel and LCL161 as neoadjuvant chemotherapy for localized TNBC was studied to investigate if LCL161 enhances paclitaxel efficacy. LCL161 is an inhibitor of apoptosis (IAP) antagonist. A TNF-α-based gene expression signature (GS) is known to be predictive of sensitivity and a higher rate of pCR with the combination was reported in GS(+) patients, but not in the GS(-) ones. Hence, it is a biomarker-driven targeted therapy for GS(+) TNBC patients. No difference was noted based on BRCA mutations [33].

IGF1-R Inhibition

IGF1-R activation results in cell proliferation and metastasis. The molecule, NVP-AEW541, inhibits IGF1R selectively and induces autophagy of TNBC cells. A study also suggested that a combination of IGF1R inhibitor and autophagy inhibitor shows a significant repression of cell proliferation and improves cell cycle arrest than when NVP-AEW541 is used alone [34].

Microtubule Disruption

Combination therapy with ixabepilone, a semisynthetic analog of epothilone B, a microtubule-targeting drug [35], and capecitabine have proven efficacious in patients with MBC, including the non-TNBC and TNBC phenotypes. EGFR is overexpressed more often in TNBC. A noteworthy correlation has also been seen between EGFR immunoreactivity and a worse prognosis in patients with triple-negative invasive ductal carcinoma of the breast. This evidence suggests that treatment with cetuximab, a chimeric monoclonal antibody specific for EGFR in combination regimens in metastatic TNBC can be beneficial. This combination therapy showed better ORR and PR than monotherapy [36].

mTOR Inhibition

A study stated that metformin activates the AMPK pathway through inhibition of complex 1 of the mitochondrial respiratory chain, which leads to the suppression of mTOR. This, in turn, results in a loss of cell proliferation and repression of glucose synthesis. Both in vitro and in vivo studies of metformin have exhibited exceptional anti-TNBC results [15]. Eribulin, which is a synthetic analog of halichondrin-B (a natural product), acts via its anti-mitotic action, leading to microtubule disruption in cancer cells, and causing G2/M cell cycle arrest. It inhibits metastasis by reversal of EMT phenotype to MET. A phase I clinical trial of a combination of eribulin with mTOR inhibitor, everolimus, provides a synergistic action, by microtubule disruption and PI3K/AKT/mTOR pathway blockade in metastatic TNBC patients that are resistant to conventional anthracycline and taxane-based chemotherapy. This combination reported modest efficacy and a tolerable safety profile [37]. A randomized phase II study of cisplatin was conducted to investigate if there is a synergistic antitumor activity on the addition of everolimus (mTOR inhibitor)

to a combination of paclitaxel + cisplatin neoadjuvant chemotherapy. Cisplatin/paclitaxel are recommended in TNBC patients who cannot tolerate a more dose-intense taxane-anthracycline regimen. Everolimus did not improve pCR, OS or provide any beneficial pathologic or clinical outcome, and had the added baggage of its toxicity [38].

Opioids

Opioids are used in cancer for chronic pain relief, but it has also been found that they can influence cancer progression and recurrence. Both agonistic as well as antagonistic opioid ligands have been found to affect both cancer growth and development. Mu opioid receptor (MOR) plays a crucial role in the progression of cancer by controlling angiogenesis, EMT, mTOR, Src, and other signaling pathways. An increase in MOR expression, or morphine, a MOR agonist, can promote the progression of triple-negative breast cancer. Whereas dezocine, a MOR and kappa receptor (KOR) mixed agonist-antagonist, targets NAMPT directly, which is a rate-limiting enzyme in the nicotinamide adenine dinucleotide pathway, ultimately causing a reduction in NAD production. The study results reported the anti-tumor effects of dezocine and it was shown to decrease cell viability, inhibit cell proliferation and colony formation, and inhibit DNA synthesis in TNBC cells in a dose-dependent manner [39].

PI3K Targeting

Alpha-basic crystallin, a small heat-shock protein, is overexpressed in TNBC and is predictive of a poor prognosis. It initiates the MAP/ERKpathway, thus, MAP/ERK inhibitors may demonstrate to be an effective therapy for alpha-b-crystallin expression [40]. FZU-0025-065, an isochroman indolenine derivative, partially inhibited AKT activation; suppressed CDK 4, cyclin D1, and cyclin B1; and upregulated CDK inhibitors- p21 and p27. It inhibits DNA synthesis and arrests the cell cycle in G1/G0 phase and has also been reported to inhibit colony formation in a dose-dependent manner [41]. Flavopereirine, an alkaloid natural extract that can also be synthesized chemically, induces cell cycle arrest and apoptosis through the AKT/p38 MAPK/ERK1/2 pathway; of TNBC cells. The levels of pAKT decreased with increasing concentrations of Flavopereirine. Downregulation of p38MAPK caused a decrease in flavopereirine-induced LC3-II accumulation [42]. Decreases cell viability. Ipatasertib, PI3K AKT pathway activation inhibitor, and paclitaxel combination are studied under FAIRLANE trial for TNBC. Furthermore, a new molecule, AZD5365, is under investigation [19]. The PAKT trial suggested that the addition of capivasertib, an AKT inhibitor/kinase inhibitor to first-line therapy with paclitaxel demonstrated a better PFS and OS in TNBC patients, particularly those having PIK3CA/AKT (activating)/ PTEN (non-activating) altered-tumors [43].

SINE Inhibition

A phase II trial tested the clinical benefit of selinexor (KPT-330), a selective inhibitor of nuclear export (SINE) targeting exportin 1 (XPO1), which is overexpressed in many cancers. It acts by retaining the normal functioning of tumor suppressor proteins by inhibiting their export from the nucleus. It is also found to cleave PARP, which may be responsible for the modest response. A recent study also reported selinexor to have anti-proliferative and anti-migratory actions by restoring arrestin-related domain-containing protein-3. It did not seem to provide an objective response, but was well-tolerated. A study has been going on to evaluate the efficacy of selinexor in combination with olaparib [44].

STAT3 Inhibition

STAT3 (Signal transducer and activator of transcription 3) controls the transcription of genes involved in various cellular functions, playing an important role in the TNBC cell progression and survival. Compared to low levels of STAT3 expression, high levels were associated with a low probability of OS. Hence, it might be a promising therapeutic target for TNBC. According to a study, pulvomycin, a novel STAT3 inhibitor, exhibits a selective reduction in proliferation of TNBC cells than normal breast cells. When pulvomycin is used with docetaxel, it shows synergistic antiproliferative activity. Pulvomycin is efficient in docetaxel-resistant cells, moreover, it also re-sensitizes them [45].

WNT5B Knockdown

It has been identified that WNT5B is one of the overexpressed genes in TNBC. Extensive levels of WNT5B in the patients were found to be related to a lower disease-free survival rate. Studies suggest that, when WNT5B is knocked down, the morphology of the TNBC cells alters from spindle to round shape with poor attachment, size of the cells is decreased; growth and the mobility are severely decreased. Knockdown of WNT5B causes noteworthy changes in mitochondria, and sufficient WNT5B is required for cell survival in TNBC cells [46].

CONCLUSION

Triple-negative breast cancer (TNBC) is a distinctive subtype of breast cancer, where the conventional therapies targeting receptors have failed to

show benefit. The abundance of information on signalling pathways could be explored to develop ways to provide better outcomes. Thus, TNBC needs to be treated as a separate entity and explicit guidelines need to be formulated, elucidating a multidisciplinary approach to therapy.

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Conflict of Interest

The authors declare that they have no conflicts of interest.

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