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Novel Ways of Targeting Triple Negative Breast Cancer (TNBC) with the Latest Research-will it Improve Prognoses

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Review Article

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Abstract

Breast Cancer, is the commonest malignancy that gets diagnosed in women, leading to the greatest cancer associated deaths all over the world. Triple negative breast cancer (TNBC) refers to the absence of estrogen, progesterone and HER2 receptors, possesses an aggressive clinical nature, having the high metastases rates. Thus here in this review we have tried to study the mechanism responsible for the high metastases rates by studying the role of Haematopoietic protein tyrosine phosphatases (HePTP) which had a crucial role in metastases of TNBC through activation of Wnt/β-catenin signaling. Further we examined, how certain regional anesthetics like ropivacaine and levobupivacaine had a protective effect in BC, roles of some novel therapies like those combining embelin (EMB)/TRAIL-HA(hyaluronic acid)/ poly(1,6-hexanediol)-diacrylate –β-5-hydroxyamylamine(PBAE)-polyethylamine (PEI) as cytotoxix and proapoptotic agents against TNBC, how regulation of miR 122-5p that causes aggression via epithelial mesenchymal transition(EMT) in TIMC via suppression of charged multivesicular body protein 3(CHMP3)through MAPK signaling might help in controlling TNBC. Further combining thiosemicarbazone compound 4 with cisplatin increased p53 phosphorylation, along with Bax level induction, as well as a decreased Bcl2 protein amounts ,increased PARP cleavage and modulated miR expression levels in TNBCs with special overexpression of miR-125a-5p ,and miR-181a-5p and thus role of miR control utilization by other way by thiosemicarbazone compound 4 targeting TNBC apoptosis might be utilized. Moreover how combining Src inhibitor dasatinib, with the PARP inhibitor veliparib, and the DNA damaging drug carboplatin in TNBC might prove effective in TNBC. Further role of DDB2 in causing resistance to PARP, combination of PARP with metabolic inhibitors is discussed. Additionally liposomes modified by fructose and RGD had >potential for forming a targeted TNBC therapy, particularly the covalently modified Fru-RGD–Lip, marking them as good liposomes having multiple functions. Thus novel therapies for TNBC which might help in developing novel therapies further for controlling TNBC has been emphasized.

Keywords: TNBC; mIR 122-5p; miR-125a-5p and miR-181a-5p; Thiosemicarbazone Compound 4; HePTP; Dasatinib

Introduction

Breast cancer (BC) represents a malignant tumor which takes place in the mammary epithelium. Recent epidemiology displays a growing incidence of BC on a yearly basis, with a trend of involving younger women [1,2]. The number of new cases have reached 16.71 million /yr, being the 1st in cancer incidence in women [3,4]. In the last 2 dceades, absolute number of BC cases has increased worldwide by 1.4times, with incidence in most countries and regions having increased by 30-40% [3,4]. In 2014, it was demonstrated that Chinese women with BC had 12.2% and 9.6% of the total new BC cases with the associated deaths, respectively [5]. The rise in incidence of BC worldwide has raised the burden regarding medical resources. Hence it is essential to conduct continuous, effective prevention and control methods on a global scale for decreasing the incidence and deaths, associated with BC.

Methods

In this review we tried to study how novel therapies could be developed for triple negative breast cancer(TNBC) and used the MeSH terms like TNBC; Metastases causes drug resistance; Prognosis; Markers for TNBC; Effective Chemotherapy; Gene markers; Role of microRNAs

Results and Discussion

We found a total of 7701 articles till sept 2019 out of which we selected 59 articles for this review. No meta-analysis was done.

Role of Baicalin Addition to Chemotherapy

BC is thought to be a disease caused by combined factors ,that are related with age, genetics, environment, lifestyle, diet, birth history, menstrual history, etc [6-8]. The treatment methods currently are based on comprehensive therapy. Once a definitive diagnosis is accomplished and proper staging along with classification as well as, surgery, radiotherapy and chemotherapy, molecular targeted therapy, endocrine therapy, biological treatment and other treatments are utilized [9-11]. But low tolerance and poor compliance related to side effects, along with drug resistance, recurrence and metastasis are still the main problems in todays BC treatment [12,13]. Specially, basal cell like forms in BC molecular typing, namely triple negative breast cancer(TNBC) that represents about 15-20% of all BC types, represents the most malignant of BC subtype s in view of its poor prognoses, early metastasis, short survival [14,15]. Thus following surgical resection and radiotherapy and chemotherapy in the early stage, to decrease the side effects of chemotherapeutic drugs and improve the quality of life, complementary and alternative medicine (CAM) has become the 1st choice of patient's mainly from East Asia. In CAM, Chinese CAM has become a well-recognized therapy in modern BC treatment programmes in view of its advantages like syndromic differentiation, safety and efficacy [16]. Chinese medicine has marked advantages of improving symptoms of advanced BC treatment programmes, increasing patient's physical Fitness, decreasing drug resistance, decreasing the post-operative recurrence and metastasis, increasing efficacy and decreasing toxicity of radiotherapy and chemotherapy [17]. Baicalin obtained from Seutellare Radix possesses anti-inflammatory, anti-oxidant, antiviral, anti-bacterial, antihypertensive, diuretic and other effects. Currently it was demonstrated that it has marked inhibitory effects on different types of malignant cells via p38 MAPK signaling pathway, β-catenin signaling pathway etc [18]. But its molecular mechanisms against BC still requires more work. Thus Yang, et al. tried to investigate the control mechanism of baicalin on TNBCs biological network using a systematic biological strategy and cytology work. Using this method for predicting the basic targets of baicalin genes collect the genes of TNBC, and evaluate the TNBC and baicalins network. Following the systematic biological, examination was done, and the cytology experiment, quantitative real time polymerase chain reaction (qPCR) was utilized to confirm the crucial biological processes and signaling pathways. Following the systematic biological evaluation 2 networks were formed and evaluated i) TNBC network ii) Baicalin–TNBC protein –protein interaction (PPI) network. Various TNBC-associated treatment related genes, clusters, signaling pathway and biological processes were determined. Experiment on cytology demonstrated that baicalin can inhibit the proliferation, migration and

invasion of BC MDA-MB-231 cells ($p<0.05$). Thus concluding that baicalin provides anti-tumor effects via controlling the targets, biological processes and pathway observed in this study [19].

Role of HePEP

Of the women who present with breast cancer, which is the maximum diagnosed cancer and the commonest cause of death related to cancer. Morbidity of BC is 11.6% and mortality is 6.6% respectively, pointing a big problem regarding women's health [20]. On the basis of presence or absence of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor (HER2), BR patients are classified into these groups i)luminal A, ii) luminal B, iii) HER2 overexpression and iv)triple negative subgroups [21-23]. BC which do not express ER or PR and absence of Erb2 receptor kinase 2(ERBB2 mostly called HER2) amplification are referred to as triple negative BC(TNBCs), that are responsible for 10-20% of total BC's [24,25]. In view of the lack of all 3 receptors, TNBC does not respond to hormonal therapy, along with drugs aiming at the HER2 protein .There is a disadvantage with respect to survival for TNBC in contrast with 93% of other BC subtypes [26]. Currently the standard therapy for TNBC is various chemotherapy regimens, yet prognosis of TNBC continues to be poor in view of continuous recurrence and metastases [27]. Those presenting with metastatic TNBC have only 1year rough median survival [9]. Hence a > insight regarding the molecular mechanisms behind the metastases of TNBC is essential for better therapy clinically.

Loss of control of Wnt/β-catenin signaling pathway takes plays in various kinds of cancers and is the basic cause of lot of herediary syndromes [28,29]. Wnt ligands bind to the Fizzled and low density lipoprotein receptor-related protein 5/6 co-receptor complex to activate the canonical Wnt signaling pathway [30]. This activated complex inactivates at functional level the destruction complex via a mechanism not clear till now that results in collection and nuclear translocation of β-catenin in the nucleus. This β-catenin in the nucleus involves T cell factor/lymphoid enhancing-binding factor (TCF/LEF) transcription factors and activates the Wnt transcriptional program [31]. Abnormal Wnt signaling is a property of TNBC subjects with both and non-canonical pathways implied in TNBC metastases and TNBC subjects showing dysregulated Wnt/β-catenin signaling have a >chance of acquiring lung and brain metastases [32]. Interaction of Wnt ligands with their receptors activates the Wnt/β-catenin signaling and consequently results in the stabilization of β-catenin. This stabilized β-catenin moves to the nucleus and stimulates various transcriptional programs that are specific and affect cellular responses, that are cellular proliferation, development, neoplasia, stem cell maintenance, invasion and migration, besides other processes [25,33,34]. Though nuclear β-catenin amount is upregulated in>50% of BC cases gene mutations that encode cellular progression might be a probable reasoning for the >amounts of β-catenin in BC [25,35]. Thus pointing that dysregulation of cellular expression might be a probable answer for the great levels of β-catenin in BC [32,36]. Hence control of the β-catenin core protein is vital for both the status of Wnt signaling in TNBC continuation, along with nuclear movement of phosphorylated β-catenin through the cytoplasm adds to metastases of TNBC [37,38].

The crucial controlling steps include phosphorylation; ubiquitination and consequent breakdown β-catenin are controlled by a committed cytoplasmic breakdown complex. This complex is made up of the central scaffold protein Axin along with 3 other core contents namely adenomatous polyposis coli (APC), glycogen synthase kinase 3 beta(GSK3β), and casein kinase 1(CK1) [30]. GSK3β is one of the best studied intracellular signaling molecules, which regulates the canonical Wnt/β-catenin pathway in the form of a ubiquitously expressed serine /threonine protein kinase [39]. Phosphorylation of GSK3β at Tyr216 residue is essential for the phosphorylation of β-catenin is well accepted and hence causes breakdown of β-catenin and resulting in inhibition of Wnt signaling [36]. A main part is played by protein tyrosine regulation in cellular physiology along with cancers [40]. Collected proof points that different protein tyrosine phosphatases (PTP's), like protein tyrosine phosphatase non receptor type 11(PTPN11) can result in de phosphorylation of GSK3β at Tyr216 residue and hence stabilizes β-catenin in the cytoplasm and resulting in progression of cancer [41-43]. But, if PTP takes part in Wnt/β-catenin signaling through regulation of GSK3β activity in TNBC is still not clear. Haematopoietic protein tyrosine phosphatases (HePTP) belongs to the PTP family which is understood to control a variety of cellular functions, that has inflammatory responses along with T cell Antigen receptor (TCR) signaling as a part [44,45]. What is not known is if HePTP takes part in BC progression.

Thus Yu L, et al. [46] aimed to explore the mode of TNBC metastases. They checked the expression of PTP, HePTP utilizing real-time PCR, Western blot. They utilized

Wound healing assay and trans well matrix assay for examining the promigration and proinvasion property of HePTP in vitro. To examine Wnt/β-catenin signaling activity they utilized Luciferase assay along with nuclear extract evaluation. They revealed that HePTP was overexpressed in TNBC and it helped in migration and invasion of tumor cells .They demonstrated that overexpression of HePTP in HePTP low expressed cells helped in promoting the migration and invasion of tumor cells with great effect. Thus their results pointed that HePTP has a significant part in the metastases of TNBC through the activation of Wnt/β-catenin signaling. Thus they hypothesized that HePTP might act as a novel prognostic marker along with a potential Target for developing therapy for TNBC.

Role of EMB/TRAIL-HA/PBAE-PEI

In view of no effective targeted therapy for TNBC, Xu, et al. [47] designed along with prepared hyaluronic acid (HA) mediated targeting of tumor along with pH –sensitive ampiphilic polymeric nanoparticles for codelivering the anticancer agent embelin (EMB) and tumor necrosis–related–apoptosis–inducing ligand(TRAIL)plasmid (pTRAIL)(EMB/TRAIL-HA/PBAE-PEI) to obtain synergistic effective anti BC therapy. The pH –sensitive ampiphilic polymeric nanoparticles were synthesized with the utilization of ampiphilic polymers polyethylamine (PEI)-poly(1,6-hexanediol)-diacrylate –β-5-hydroxyamylamine](PBAE), that was formed through Michael addition polymerization. Utilizing the benefit of the specific binding that occurs between HA and CD44 that is markedly expressed in MDA-MB-231 TNBC cells in comparison to MCF-7 non TNBC cells having lower CD44 expression. Furthermore EMB/TRAIL-HA/PBAE-PEI showed increased cytotoxic as well as pro-apoptotic effects against MDA-MB-231 cells in contrast to free EMB and EMB or pTRAIL loaded nanoparticles through activating caspase 3/7 increase in reactive oxygen species(ROS) levels, and inhibiting the apoptosis related protein expression. Thus concluding that EMB/TRAIL-HA/PBAE-PEI caused increased cytotoxic as well as pro-apoptotic effects against MDA-MB-231 cells and demonstrated higher role in TNBC therapy.

Role of Local Anaesthetics in Protection against BC

Various retrospective trials have demonstrated a potential protective action of regional anaesthetics in decreasing cancer recurrence following surgery if indicated. Thus earlier it has been shown that a protective action of anaesthetic agents in BC cells and in other types of cancer exists. Conversely, how anaesthetic agents affect cancer requires > study. In view of that Castelli, et al. [48] utilized 2 separate human cancer line, MDA-MB-231, TNBC and A375, melanoma for their study. With the use of Western blotting, immunofluorescence and terminal deoxy nucleotidyl transferase DUTP nick end labeling evaluation, they evaluated the signal transduction pathways which got activated with the anaesthetic agents, like ropivacaine and levobupivacaine. Both ropivacaine and levobupivacaine counteracted cell proliferation by positive modulation of cell death signaling and by decreasing cell proliferation and cell survival pathways [48].

Role of miR-122-5p and Charged Multivesicular Body Protein 3(CHMP3)

With TNBC being very metastatic and usual poor prognosis along with absence of much understanding of TNBC and gene therapy targets very limited efficacious therapy for TNBC has been made. Wang Z and Wang X [49] in an attempt to get insight the molecular mechanism behind progression of TNBC carried out a study to understand the promising gene therapy targets for TNBC. The effect of miR-122-5p's binding charged multivesicular body protein 3(CHMP3)3'-untranslated region (3'UTR) on TNBC cells was evaluated , in vitro studies quantitative real time polymerase chain reaction, immunoblot analysis, dual luciferase reporter gene assay, cell counting assay, transwell invasion assay along with flow cytometry-determined cell apoptosis assay were used. Further utilization of Target Scan Human 7.2 database to find out the target correlation between miR 122-5p and CHMP3 3'UTR. They utilized timer algorithm to give an overview of the expression of CHMP3 gene across human-pan-cancer, for predicting the survival outcome of BC patient's, and to predict the association between CHMP3 gene expression and epithelial mesenchymal transition (EMT) and mitogen activated protein kinase (MAPK)-related gene expression. Significant down regulation of CHMP3 gene was observed across a broad range of human cancers that included BC (BRCA). A> amount of CHMP3 gene predicted a better 3-5 year survival in subjects with BRCA. In their studies miR-122-5p was significantly unregulated, with significant down regulation of CHMP3 in TNBC cells as compared to normal cell line. miR-122-5p simulates increased TNBC cell viability, proliferation and invasion while upregulation of CHMP3 gene caused opposite result. Expressing miR-122-5p forcibly suppressed cell apoptosis, forced EMT and MAPK signaling while forcing expression of CHMP3 caused the

reverse. Hence their conclusions were that miR-122-5p stimulates aggression and EMT in TIMC through suppression of CHMP3 via MAPK signaling.

Role of Thiosemicarbazone Compound 4 Combination with Cisplatin and MiR's

With the absence of ER, PR, HER2 in TNBC, an aggressive clinical phenotype is found that is responsive to chemotherapy, but not to hormonal or targeted immunotherapy. For recognizing potent and selective anti-TNBC drugs, a set of thiosemicarbazone derivatives were screened to check their cytotoxic activity against MDA-MB-231 breast cancer cell line by El-Majzoub, et al. [50]. They used MTT assay for evaluating cell viability. Further they evaluated, P53 phosphorylation status, poly (ADP-ribose) polymerase (PARP) cleavage along with Bcl2 and Bax protein levels utilizing Western blot. For characterizing miR expression amount, quantitative real time polymerase chain reaction was done. Combination of cisplatin with thiosemicarbazone compound4 displayed high anti-TNBC ability. Marked increase in p53phosphorylation, along with Bax level induction occurred on the combination of cisplatin with compound4 as well as a decreased Bcl2 protein amounts, increased PARP cleavage and modulated miR expression levels in TNBCs with special overexpression of miR-125a-5p, and miR-181a-5p. Interestingly, miR-125a-5, and miR-181a-5p, could lead to significant downregulation of BCL2 expression by binding to their target sites in 3'UTR. Thus together their results showed an anti-TNBC activity of cisplatin with thiosemicarbazone compound 4 combination gets mediated through apoptosis induction [50].

Role of Combination of Dasatinib, Veliparib and Carboplatin

Combination of PARP inhibitor with a DNA damaging drug has demonstrated good effect for therapy of TNBC, but not all patients are responsive to this combination. Multiple cancer cell properties get controlled via Src protein kinase which has a crucial part in tumorigenic processes. But Src inhibitors as single drugs have demonstrated minimal effects in solid tumors. Sun, et al. [51] evaluated the antitumor effects of the Src inhibitor dasatinib, the PARP inhibitor veliparib, and the DNA damaging drug carboplatin in TNBC models for finding the combination having that maximum clinical application. They tested dasatinib, veliparib and carboplatin in TNBC cells in vitro and in xenograft tumors in vivo. Interestingly therapy with the combination of veliparib and carboplatin led to an increase in phosphorylation. Dasatanib prevented the overexpression of Src that was induced by veliparib and carboplatin and moreover inhibited the downstream signaling of Src. In xenograft models, the combination of al 3 dasatinib, veliparib and carboplatin displayed > tumor growth inhibitory outcomes in comparison with single agents or double combinations. Systematic toxicity was not seen in mice treated with this 3 agent combination. Thus concluding that combination therapy with dasatinib, veliparib and carboplatin is efficacious in TNBC clinical trials [51].

Role of DDB's in PARPi Resistance

Although PARP inhibitors (PARP is) have demonstrated good therapeutic efficiency in TNBC patients, in the end resistance develops, that prevents getting a cure. A lot of research has shown how diverse the mechanisms are behind the PARP i sensitivity of BC. Zhao, et al. [52] showed that DDB2, that is a DNA damage recognition factor, might protect TNBC cells from PARP i by controlling DNA double stranded break repair through homologous recombination pathway, while the depletion of DDB2 sensitizes TNBC cells to PARP i. Moreover they revealed that DDB2 could sensitize Rad 51 through physical association and disrupting the ubiquitination pathway-induced proteasomal degradation .Thus concluding that there is a necessary part played by DDB2 in modulating homologous recombination pathway activity, which pointed to a future target for TNBC treatment.

Role of PARP with Metabolic Inhibitors

Cancer transformations markedly change metabolism of the cells by raising utilization of glucose through glycolysis for supporting tumorigenesis [53]. Reda, et al. [54] verified that in comparison to ER positive cells (MCF7), TNBC cells (MDA-MB-231) have a higher dependence on glycolysis and thus provide a basis for targeting these cells utilizing glycolytic inhibitors. Indoacetate (IA), an effective GADPH inhibitor led to approximately 70% reduction in MDA-MB-231 cell viability at 20μM, in contrast to 40μM IA being required to reduce MCF7 cell viability only by 30% within 4h of treatment. But the triple negative cells displayed high capacity to recover following 24h, while MCF7 cell got totally removed at concentrations <10μM. For getting insight into the survival of MDA-MB-231 cells, they studied the metabolic interferences related to both acute as well as prolonged therapy with IA. Those TNBC cell populations that had resilience displayed a markedly

higher count with active mitochondria, lesser apoptotic markers, normal cell cycle regulations, moderately decreased ROS, but a rise in mRNA levels of p27 and PARP 1, all which had compatibility with increased cell survival. Thus his results emphasized that there was an interrelation between PARP and mitochondrial oxidative phosphorylation in TNBC, which comes into part once there is interruption of glycolysis. Keeping these results in mind, they pointed that utilization of combination of treatment with PARP and mitochondrial inhibitors might act as a novel therapeutic option for TNBC.

Role of Liposomes

Currently chemotherapy and radiotherapy are the major methods used for treating TNBC, known for bad prognosis and >rate of deaths. 2 kinds of dual targeting TNBC liposomes (Fru-RGD –Lip and (Fru +RGD –Lip) that is novel and actively recognizes fructose transporter $GLUT_5$ and integrin $\alpha_v\beta_3$, got designed and made for the study by Pu, et al. [55]. Initially, a Y shaped Fru-RGD–chol ligand, in which a fructose along with peptide Arg-Gly-Asp (RGD) got covalently attached to cholesterol, and their design made and then manufactured. After that, the Fru-RGD–Lip was synthesized by putting Fru-RGD–chol into liposomes and Fru+RGD–Lip was constructed by adding both Fru- chol and RGD –chol (having a molar ratio of 1:1) into liposomes. Particle size, zeta potential, efficiency of encapsulation and stability of serum of the paclitaxel–loaded liposomes were defined. Results pointed that paclitaxel –loaded Fru+RGD–Lip possessed the maximum growth inhibition against $GLUT_5$ and integrin $\alpha_v\beta_3$, overexpressed MDA-MB-231 and 4T1 cells. Uptake of Fru-RGD–Lip by cells on MDA-MB-231 cells and 4T1 cells was 3.19 and 3, 23 –times >than of the uncoated liposomes (Lip). Uptake of Fru+RGD-Lip was a little bit less, providing a 2.81-and 2.0-2.90-reduction than of Lip in 2 cell lines, respectively. Thus this report showed a mechanism that cellular uptake of dual targeting TNBC liposomes, both had chances of getting recognition and brought on about through $GLUT_5$ and integrin $\alpha_v\beta_3$ initially, and then getting endocytosed via comprehensive paths in an energy–based method. Furthermore, Fru-RGD–Lip showed the most accumulation, that was 2.62times > as compared to Lip for example, at the sites of tumor as compared to other liposomes utilizing in vivo imaging. Together, the liposomes that were modified by fructose and RGD had marked potential for forming a targeted TNBC therapy, particularly the covalently modified Fru-RGD –Lip, marking them as good liposomes having multiple functions.

Role of hsa- miR-4756-3p

Abnormally expressed mRNAs and miR's, both have an important part in cancer cell function that makes integration analysis tough. Gu, et al. [56] 1st applied master regulator analysis algorithm and verified hsa-miR-4756-3p as a candidate miR in TNBC patients, and found hsa- miR-4756-3p might control TNBC cell line apoptosis, proliferation, migration as well as cellcycle along with TGFβ1 signaling and antitumor growth. In TNBC, fork head box protein M1 (FOXM1) was observed to be a target gene, with knockout of FOXM1 totally abolished hsa- miR-4756-3p induced cell migration and metastases, TGFβ1 signalling and epithelial mesenchymal signal activation, that suggested that hsa- miR-4756-3p acts through FOXM1- TGFβ1-EMT exist.

Role of BRCA 1siRNA-Pro-Pt

In view of powerful DNA repair and absence of expression of surface antigens, TNBC is insensitive to chemotherapy or endocrine therapy that demands an immediate effective strategy for bettering the prognosis. Dong, et al. [57] introduced DNA repair blocker BRCA1 interfering RNA (siRNA) with cisplatin (Pt) into the enhanced designed pH sensitive shell-core platform for increasing the chemotherapeutic effect by silencing the DNA repair associated gene. BRCA1 siRNA and Pt prodrug (Pro-Pt) on this platform got independently encapsulated in the porous outer shell and hydrophobic inner core with very good encapsulation efficacy along with being stable that abrogated the breakdown at the time of circulation. Appropriate size and urokinase plasminogen activator analogues (uPA) having great affinity for uPA receptor (uPAR) showed very good double passive and active tumor targeting capacity .Furthermore the exposed PEG hydrophobic chain prevented the nanoparticles (NPs) from precipitating by serum proteins or inactivating by nuclease in the blood cycle. Specially, the degradable CaP (calcium ions and phosphate ions) shell with smart pH sensitivity would dissipate from the NPs present in the lysosomes => bursting of the lysosomal membranes, which guarantees the escape of lysosomes and the subsequent release of the siRNA and Pro-Pt, while the BRCA1 siRNA blocked the DNA repair pathway, that was followed by decrease of Pro-Pt to Pt for irreversible DNA damage. Thus the uPA-SP@ CaP NPs gives a good method for treating TNBC with great efficiency and getting more hope for TNBC subjects.

Role of miR205/ ZEB1/ Ki-67/ LRG1 Axis in SETD1A

With chemoresistance becoming a problem in TNBC, it is key to find the correct treatment regimen by getting insight into the molecular mechanisms of driver controllers that are responsible for the progression of TNBCs. Mohammed Hanif [58] aimed to get insight into the Control of probable mechanisms in the formation of TNBC in 2 TNBC cell lines. SETD1A was transiently transfected in MDA-MB-468 (FEC good prognosis) and Hs 578T (FEC poor prognosis). Control of probable targets miR205, EMT markers ZEB1 and LRG1 and proliferative markers Ki-67 were tested by RqPCR for finding the SETD1A interactions. This study showed marked recovery of miR205 with removal of SETD1A and decrease of ZEB1 in MDA- MB-468. But there was no change in Hs 578T that suggested that control of ZEB1 might be completed by other modes which are related to aggressive cell line properties and the expression of endogenous ZEB1 was high in relation to Hs 578T. Increase of LRG1 and reduction in Ki-67 were seen when SETD1A was knocked down. Greater expression was seen by LRG1 in Hs 578T and not in MDA- MB-468, pointing that LRG1 aided in special poor FEC outcomes in TNBCs. Basic mechanism of SETD1A in miR205/ ZEB1/ Ki-67/ LRG1 axis requires future testing. If blocking of this pathway is actually related to transcriptional or post transcriptional activation in TNBC cell line models, proper checking in clinical samples is needed for achieving the prognostic as well as treatment value in TNBC's.

Chemotherapy in Obstructive Jaundice Secondary to Metastases

Metastatic BC presenting with obstructive jaundice secondary to para aortic lymph node enlargement is uncommon presenting a challenge for treatment. Sattwika, et al. [59] presented a 61 yr old woman with TN left invasive ductal BC with liver and pulmonary metastases. After getting gemcitabine and carboplatin as the 4th-line therapy, chemotherapy had to be deferred in view of a rise in serum bilirubin levels. On abdominal imaging para aortic lymph node Metastasis that was compressing distal common hepatic duct was revealed. Capecitabine along with ursedeoxycholic acid for 8 cycles was administered. Her jaundice got resolved following 8 cycles, and on radiology complete resolution of obstructive jaundice was demonstrated. Thus stressing on the success of Capecitabine regimen as a salvage treatment in a Metastatic BC subject with hyperbilirubinemia and helps in getting best systemic chemotherapy for Metastatic obstructive jaundice where there are limited facilities available.

Conclusion

Thus here we have highlighted the importance of using HePEP as a prognostic marker along with therapeutic target for TNBC. Further role of CAM like Baicalin combination might be helpful in tolerating chemotherapy. Further roles of various regional anaesthetics as protective agents, other methods of utilizing certain miR's might help in developing novel therapies like MiR-121-5p, further role of DDB2 in PARP resistance and combination of PARP with metabolic inhibitors might be helpful in preventing PARP resistance .Moreover addition of Src inhibitor with the PARP inhibitor veliparib, and the DNA damaging drug carboplatin in TNBC might be of help. Furthermore other novel combinations tested for developing promising prognostic markers and delivery through different liposomes and other combinations might be utilized. A case of successful use of Capecitabine in a case of obstructive jaundice secondary to metastases is described.

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