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Triple-negative breast cancer: challenges and treatment options

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ABSTRACT

TNBCs or Triple negative breast cancers are characterized by the deficiency of progesterone and estrogen receptors and also the absence down regulation of Human epithelial growth receptor type 2 (HER2). TNBCs have low prognosis rate because of heterogeneity. The heterogeneous nature of this cancer has constrained the effective progress in drug targeting among certain people. In general HER2, PR and ER and the rate of proliferation are main predictive and prognostic factors in the detection of cancer of breast. Several pathways are involved in the progression of triple negative breast cancer from basal like cancer cells. The foremost being the loss by BRCA1-mediated pathway or mutation in the expression of several receptors. Certain groups have made some progress in unwinding TNBC's biological diversity and relating patterns of gene expression to molecular or genotypic subtypes. Earlier molecular categories of breast cancer use PAM50 via gene expression analysis to separate the breast cancer into the 4 intrinsic subtypes classified among many TNBCs in basal (BL) group and others divided between HER2 and luminal rich group. Currently, targeted therapy for TNBCs has not been approved. Nonetheless, there is continuous progress been made to detect the tumors at specific site for targeting and establish novel improved therapy. This review speaks about different approaches to TNBC treatment like cytotoxic therapy, targeted strategies, and chemotherapeutics by damage to DNA and targeting for repair of DNA and potent Nano carriers for targeting TNBC.

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INTRODUCTION

Breast cancer is a complex heterogeneous disease (Lyden *et al.*, 2011). It is classified into the human epithelial growth receptor type 2, Claudine-low, luminal A, luminal B and basal like cancer. All the subtypes are capable of metastasizing to distant organs by the involvement of distinctive pathway with favored metastatic locations, and different responses to survival after recurrence. Biological breast cancer subtypes are identified on the basis of expression profiles of gene immune-histochemical (IHC) (Gerratana *et al.*, 2015) and presence of biomarkers. In general HER2, PR and ER and the rate of proliferation are main predictive and prognostic factors in the detection of cancer of breast. Depending on the subtypes, local and systemic treatments are chosen accordingly.

The tumors in the breast may spread to other body sites by metastasis. Approximately 6.2 to 61 percent of patients with breast cancer were diagnosed with Metastatic breast cancer (MBC). Metastatic breast cancer is the 2^{nd} largest reason for mortality amongst women in US. Age, ethnicity, endoge-

nous hormones, menopause, cell histology, smoking, rate of metastasis, period of breast feeding, mutation and underlying biology of tumor such as primary grade of tumor and dimension may increase chance of MBC incidence. The major cancer sites to spread include the bones, lungs, soft tissue, liver and adrenal gland (Torres *et al.*, 2015).

Triple-negative breast cancer

Several pathways are involved in the progression of triple negative breast cancer from basal like cancer cells. The foremost being the loss by BRCA1-mediated pathway or mutation in the expression of several receptors. 10 – 20% cases of the breast carcinoma is constituted by TNBC with decreased PR, ER and HER2 expression. TBNC metastasis is a multifaceted process characterized by genetic and epigenetic changes, angiogenesis, stroma-tumor interactions, intravasation through the basal membrane into blood or lymphatic vessel, circulation subsistence and extravasation. The response by patients suffering from TNBC during HER2-targeted endocrine therapy is comparatively low which develop a need for novel treatment options. Additionally, the resistance in TNBC to conventional treatments increases due to overexpression of TNBC-specific EGFR protein (as compared to other breast cancer subtypes) Hence, this protein's suppression will theoretically improve the effectiveness of TNBC therapy. siRNA targeting at EGFR mRNA is of importance. Naked siRNA is unstable in the bloodstream and in tumors and also has low penetration rate at tumor site. Thankfully, nanotechnology can be employed to deliver siRNA efficiently as well as traditional anticancer treatments within TNBCs (Khan *et al.*, 2019).

Breast cancer - molecular classification

Certain groups have made some progress in unwinding TNBC's biological diversity and relating patterns of gene expression to molecular or genotypic subtypes. Earlier molecular categories of breast cancer use PAM50 via gene expression analysis to separate the breast cancer into the 4 intrinsic subtypes classified among many TNBCs in basal (BL) group and others divided between HER2 and luminal rich group. The basal breast cancers had extremely proliferative property and many of them show reduction in BRCA 1 & 2 function. Mutation carriers have shown sensitivity to drugs that cause double-stranded DNA breaks (DSBs) like alkylating agents or polymerase (ADP-ribose) polymerase (PARP) inhibitors when BRCA1 & 2 are combined in homologous recombination (HR). Identifying the fifth intrinsic subtype further refinement was done. Having lesser poliferative property compared to basal like tumors, Claudine low subtype for expression of tumor-initiating genes as well as mesenchymal genes. The triple negative status was found by using the data from analysis of HER2, ER and PR. The TNBC disease is reclassified to identify approximately seven distinct molecular subtypes exhibiting specific gene expression and ontologies in Figure 1. It was found that different targeted therapies can react differently to eachsubtype on in vitro as well as in vivo assessment (Kriege *et al.*, 2012). The subtypes described included basal 1, basal 2,), cell-like mesenchymal (MSL), mesenchymal (M), luminous androgen-like (LAR), unclassified subspecies and immunomodular (IM).Further subtle transcriptional differences among TNBCs have been discovered including BL group subtypes and androgen receptor. By this study, an improved understanding of TNBC's complexity offers the opportunity to develop new therapeutic approaches. Many findings concentrated on recognizing somatic mutations in breast tumor using next-generation sequencing, including the Cancer Genome Atlas (TCGA), which had previously recognized gene mutations involving breast cancer. Subtype of luminal A showed weakest mutation rate whereas basal like and HER2 enriched subtypes was observed the strongest. Despite low PI3Kmutation rate, high activity of PI3K and high mutation rate of TP53 was observed in basal type (The Cancer Genome Atlas Network, 2012). Figure 1 depicts intrinsic subtype PAM50 and subtype TNBC.

Understanding tnbc heterogeneity

The emergence of heterogeneity in responses during the treatment of TNBC along with long term effects prior the molecular profiling have been demonstrated from the clinical data. Few patients show complete pathological response (pCR) during surgery as well as they react very well to neoadjuvant chemotherapy and experience quick recurrence following surgery. The predictable features to detect patients showing pCR can't be presented as well as those who can't respond to chemotherapy. High-grade invasive ductal carcinomas are the vast majority of TNBCs except for some cases where the tumors are histologically distinct, for example adenoid cystic carcinoma, medullary carcinoma, and metaplastic carcinoma and secretory carcinoma and the prognosis of these carcinoma depends on the pathology (Lehmann and Pietenpol, 2014).

Six methods of testing primary BCs were used by the Cancer Genome Atlas Research Network: DNA methylation, exome sequencing, genomic DNA copy-number arrays, microRNA sequencing, messenger-RNA arrays, and reverse phase protein array.

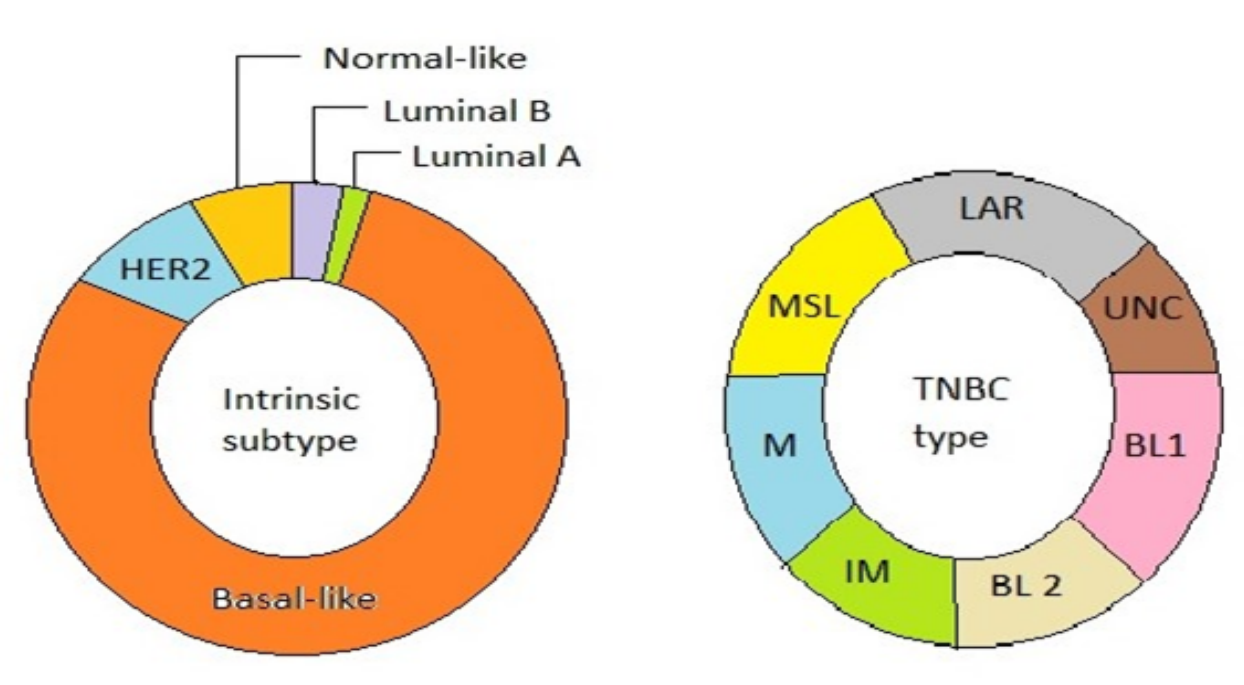

Figure 1: Intrinsic subtype PAM50 and subtype TNBC

Somatic mutations occurred in only three genes across all BCs at a point greater than 15 per cent: TP53, PIK3CA, and GATA3.In some subtypes of BC unique mutations are more common. The most common observations for TNBC / BL cancers have been the loss of BRCA1, PIK3CA, RB1 and TP53. Identified generators, such as PIK3CA, PTEN and P53 have the maximum frequency of cloning, however some patients show less cloning frequency during diagnosis whilst some show additional comprehensive clonal development, demonstrating more substantial TNBC heterogeneity (Shah *et al.*, 2012).

Subtyping TNBC: clinical implications

The profiling of expression in TNBC gene can be described in six separate subtypes: BL1 and BL2 (basal like1 and basal like 2), a mesenchymal subtype, an immunomodulatory (IM) subtype, mesenchymal stem (MSL) subtype, and a subgroup of the luminal androgen receptor (LAR). The advantages of this research were to further classify the molecular markers in the equivalent cell lines to offer pre-clinical stages in progress of successful therapy. BL1cell lines are utmost susceptible to Cisplatin as well as the mesenchymal and MSL cell lines are much sensitive to an Abl / Src inhibitor, Dasatinib. The genomic subtype, genetic abnormalities and its potent therapeutic targets are mentioned in Table 1.

A similar community made use of the intrinsic subtype technique for knowing the nature of every TNBC subtype. It was found entire subtypes of TNBC excluding MSL and LAR to be constituted predominantly by the same intrinsic subtypes of BL (BL-1 [99.02%], BL-2 [95.11%], Immunomodulatory [84.03%] and mesenchyme subtype [97.4%]).The subtype, LAR is categorized into HER2 (74.03%) and luminal B (14.05%), and also MSL comprises of BL (50.01%), normal like (28.2%), and luminal-B (14.01%).

Further analysis of genetic expression showed a type of the Claudine-low tumor. Molecular characterization has shown for the tumors to undergo EMT (epithelial to mesenchymal transformation), immune system response, and stem-like features, but have low luminal and proliferation-associated gene expression (Prat *et al.*, 2010).

TNBC's comprehensive analysis gives rise to better choice of target population which are most likely to respond to specific treatments. Molecular subtypes of TNBC, for example, may react differently to CT. A retrospective review of neoadjuvant CT and its response did confirm the clinical relevance of the genomic class.

Heterogeneity assessment in Triple negative breast cancer and grouping leads to various targeting therapies in mere future. Possible strategies are DNA damage and repair, modulation of immune system and hormone-receptors as well as inhibition of the signal pathways.

Potential clinical trial helps in better understanding the need for subtyping in predicting pCR and long-term effects among patients. For subtypes with

Table 1: The genomic subtype,genetic abnormalities and its potent therapeutic targets

Types	Gene abnormalities	Potent therapeutic target
BL1 subtype	· Abnormalities in gene expression during cell cycle · DNA repair gene (ATR–BRCA pathway) and genes responsible for proliferation	· PARP inhibitors · Genotoxic agents
BL2 subtype	· Alteration in glycolysis, gluconeogenesis, Myoepithelial marker expression · Genetic abnormalities leads to variation in growth factor signaling pathways of EGFR, NGF, IGF-IR, Wnt/β-catenin MET, NGF and IGF-1R.	· mTOR inhibitors · Growth-factor inhibitors
IM subtype	· Gene signature for medullary BC (rare TNBC with a favorable prognosis) · Immune cell processes (CTLA4, IL12, IL7 pathways, antigen processing/presentation)	PD1/PDL1 inhibitors
Mesenchymal stem-like	· Angiogenesis genes · Similar to M · Low proliferation	· PI3K inhibitors · Antiangiogenic therapy · Src antagonist
Mesenchymal-like	· Growth factor signaling · EMT · Cell differentiation · Cell motility	· EMT- and CSC-targeted treatment · mTOR inhibitors
Luminal androgen receptor	· Luminal gene expression pattern · Molecular apocrine subtype · Androgen receptor gene	Anti-androgen therapy

reduced therapeutic response to average CT, new therapeutic strategies are needed.

Treatment and challenges of triple negative breast cancer

Cytotoxic therapy

For operable and advanced breast cancer cytotoxic chemotherapy can be used as a foundation of treatment. Antibutulins, anthracyclines, alkylating agents, anti-metabolites and platinum agents can be used for advanced as well as localized anti-cancer activity.

Normally an alkylating agent like cyclophosphamide and epirubicin or doxorubicin is given simultaneously with taxane, then record the highest pathological response (Pcr)which showed the least recurring rates were observed in adjuvant setting. Few research were specifically designed to test novel therapeutic strategies in TNBC, and those documented or under way are listed below (Dai *et al.*, 2016).

Antitublin therapy

Retrospective and subgroup analysis were performed to find the role of antitubilin agents in Triple negative breast cancer. For example, a study of 400 observable disease patients participating in 2 Phase III randomized trials contrasting ixabepilone plus capecitabine with capecitabine alone found progress in response rate, however no change in overall survival across the 450 patients. The 310 research did not show an improvement in overall survival among 1112 patients with taxane-pretreated and antracycin-treated breast cancer compared to capecitabine in patients with disease following up to two prior chemotherapy regimens for metastatic disease, although the 295 patients with triple negative breast cancer had improved overall survival with eribulin in a controlled subgroup (Hugh *et al.*, 2009).

Platinums

The use of Pt entities in the treatment of MBC (metastases of breast cancer) has been tested lately. In patients with advanced TNBC, some retrospective analyzes also suggested improved survival

with platinum-based CT. The prospective Phase II study among 85 patients found activity of Pt-Carboplatin (6/3-week curve) and Pt-Cisplatin (75 mg / m2/3 weeks) in MTNBC patients, particularly in patients with BRCA1/2 (gBRCA1/2) mutations. The response rate was 25.61 percent which increased to 54.52 percent in patients with germline mutation of BRCA1/2. Interestingly it was found that the patients with no mutation where much benefited from Pt based therapy by the application involving measure of function of DNA repair. Further studies demonstrated that in spite of absence of mutations of germ-line, these patients who presented greater response to this assay showed good response to Pt therapy (Balko *et al.*, 2012).

San Antonio Breast Cancer Symposium (SABCS) held during 2014 proposed a potential randomized study consisting of docetaxel with carboplatin in TNBC patients. Responses obtained from randomized TNBC patients with mutation in BRCA1/2 gene stated considerably greater response and increased PFS (Progression Free Survival) relative to docetaxel in combination with carboplatin.

Early TNBC

In TNBC (±30 per cent) the incidence of luminal breast cancer is lower compared to pCR after anthracycline- and taxane-based neoadjuvant chemotherapy. Compared to patients who do not have pCR at the time of surgery , patients with pCR after neoadjuvant chemotherapy usually provide a better diagnosis. ([i]). New therapies must be assessed after neoadjuvant CT in patients with residual disease. Once cisplatin is applied to the neoadjuvant procedure, retrospective research has suggested better results in terms of pCR.For germline BRCA1-mutation carriers who received neoadjuvant cisplatin therapy the highest pCR rate was recorded.

Pt based drugs can't be applied in early TNBC Treatment guidelines, however their influence must be examined in some particular cases, like TNBC patients with a high threat of recurrence. In absence of pCR, involvement in clinical trials throughout the neoadjuvant and post-neoadjuvant setting is suggested to improve appropriate systemic standard therapy for triple negative breast cancer (von Minckwitz *et al.*, 2012).

Pharmacodynamic biomarker for drug resistance and therapy response

Heterogeneity of the tumor has been identified as a significant factor to the resistance acquired and a significant obstacle to restorative therapy. Although colonies with sensitive tumor cells can be eliminated, the residual tumor cells could be specifically enhanced, which often vary from sensitive cells genetically and histologically. Also there is proof that certain cytotoxic agents can facilitate epithelial-to-mesenchymal transition (EMT) / enhance metastasis for tumor cells, while other agents could counteract EMT and thus suppress metastasis.Kinase resistance inhibitors is sometimes facilitated by hard-wired feedback loops adapting for change in the operation among a signaling network. While receiving pCR after NAC is linked with a favorable prognosis, the prognosis for patients with residual cancer is uncertain, and differs by molecular subtype. In patients with severe residual disease, the 5 year relapse rate is considerably greater than patients with or without a negligible remaining disease after NAC, particularly in ER -ve disease. There might be possibilities to assess leftover disease qualities with a view to tailoring particular treatments for patients who stay at higher risk (Symmans *et al.*, 2007).

Targeted strategies

A number of previously focused treatments are currently under development for TNBC. There are currently a number of tailored treatments under development for TNBC. For e.g., subtypes basal like 1 and basal like 2 have better DNA reaction gene expression and cell, so optimally react to cisplatin. M and MSL subtypes are abundant in the pathways of EMT and growth factor and are receptive to rapamycin (mTOR) and PI3K / Akt / mammalian target inhibitors of abl / src and the LAR subtype is sensitive to anti-androgens.

PARP inhibitors

DNA damage can be detected and repaired by PARP which is a key nuclear enzyme. DNA single can activate the PARP nuclear enzymes which results in the poly (ADP-ribosyl) ation of other nuclear DNA-binding proteins which helps in DNA repair and survival (Amé *et al.*, 2004). Exquisitely sensitive to PARP1 inhibition are cells with defective HR (BRCA1 or BRCA2 mutant);Hypothesized as ' synthetic lethality, ' i.e. inhibit the prevalent repair pathways of DNA that lead to increased death of cells. Preclinical and clinical results have substantiated this hypothesis, so that PARP is a potent therapeutic target for TNBC. In Phase II trialsIniparib has shown PARP inhibition activity. From this positive results phase III trial was conducted in 520 patients with triple negative breast cancer, however it failed in achieving the positive endpoint. From recent studies it was found that iniparb was functionally different from other PARP inhibitors and also shows weak PARP inhibition property (Farmer

et al., 2005). It also showed cytotoxic effect in cancer cells by changing the metabolism of reactive oxygen species. The principle of targeting PARP to induce ' synthetic lethality ' will therefore still be seen as evidence of more exploration / clinical development; and with a drug that is an efficient PARP inhibitor in vivo.

Early-stage clinical trials have shown Olaparib, an oral PARP inhibitor, to be effective and safe. Olaparib was very well tolerated in a Phase I trial reinforced with BRCA1/2 mutation carriers and PARP inhibition with antitumor activity associated with BRCA1/2 mutations were also demonstrated. The findings of Phase II multicenter randomized study involved 55 patients with compromised BRCA1/2 give promising prototype and indicate a beneficial therapeutic index for a novel targeted treatment approach in patients with tumors with BRCA1/2-associated DNA repair genetic loss of function (Patel *et al.*, 2012).

Histone deacetylase inhibition

Dynamic process of deacetylation and acetylation causes transcription of gene and remodeling of chromatin which is controlled by Histone deacetylases (HSACs) enzymes. Histone deacetylases inhibitors demonstrated activity in preclinical models of TNBC.Amid such successful preclinical data, a Phase II randomized trial research of 60 patients with triple negative breast cancer was carried out. HDAC inhibitors cause genome-wide results, such as enabling re-expression of ER, or BRCA1/2, which can be followed by quieting of additional genes with tumor suppressive functions,it thus hides the potential benefit of an anti-tumor.Attempts are ongoing to classify which classes of Histone deacetylases control gene-promoting tumor populations, and to develop therapeutic agents for these particular classes (Connolly *et al.*, 2010).

PI3K-AKT-mTOR pathway inhibitors

The inhibition of the PI3 K and downstream AKT and mTOR has been recognized as important therapeutic targets due to their documented hyperactivation and involvement in various tumorigenic processes in multiple malignancies.The TCGA established stimulation of the PI3 K pathway as normal in TNBC BL breast cancer, either directly via PI3KCA mutations or indirectly via PTEN loss and/or INPP4B loss. Laboratory studies showed that inhibiting the PI3 K pathway contributes to temporary quiescence in TNBC. Preclinical results confirm efficient inhibition of the PI3K / mTOR pathway in TNBC subsets M and MSL. Integration of the PI3 K inhibitor with a PARP inhibitor has been presented to result in vivo synergy for BRCA1-related breast cancer treatment of an endogenous mouse model. Integration of the PI3 K inhibitor with a PARP inhibitor has been shown to result in vivo synergy for BRCA1-related breast cancer treatment of an endogenous mouse model (Juvekar *et al.*, 2012).

Androgen receptor antagonists

The significance of targeting the androgen receptor was based on gene profiling expression that identified a subset of TNBCs through an activated hormonally regulated transcriptional system and AR expression. Such results established the basis for a single-arm Phase II trial of non-steroidal anti-androgen bicalutamide in IHC-positive TNBC AR patients; 10 per cent of > 450 patients screened had AR expression and 19 per cent of 6 months CBR had bicalutamide. It is debatable where this study provides the proof of concept and where the modest occurrence could well be attributed to the indolent existence of the luminal disease (Tate *et al.*, 2012).

DNA-damaging chemotherapy and DNA repair targets

BRCA1 mutation and "BRCAness"

Numerous external factors and internal factors such as Oxidation reaction and hydrolysis, ionizing radiation, ultraviolet light, chemical substances, CT or metabolites have an impact on double-stranded DNA.Mechanisms for DNA repair are important to maintain the genome's stability and integrity, along with restoration of nucleotides and excision of base, recombination of homologous chromosome, end joining, repair of mismatched gene, and metabolism of telomeres. If any abnormalities are inherited in one among the genes as observed in BRCA1 or BRCA2 syndrome, can lead to cancer. Mechanisms for DNA repair are known as single- or double-stranded damage repair. In the homologous recombination process, BRCA-1 and BRCA-2 proteins are essential when damage causes breaks in both DNA strands. Further vital cellular progressions like control of cell cycle and DNA transcription, have involved the proteins as well.

As shown by IHC and genomic tests, breast cancer in BRCA-1 germ frequently shows a triple negative phenotype. The concept of BRCA was developed since there is resemblance of sporadic TNBC to BRCA-1 type cancers. Epigenetic mechanisms incapacitate BRCA-A in sporadic type of cancers. Epigenetic mechanism is characterized by irregular cytosine methylation in CpG di nucleotides .Conversely, tumors with BRCA2 are devoid of a phenotype (Lips *et al.*, 2013).

Information pertaining defects in the repair of DNA system contributes to certain different TNBC

therapy. Such tumors may be more susceptible to the chemicals (Pt) having detrimental effects on DNA. The idea of "synthetic lethality" is also tested in the laboratory, with the design of drugs (poly ADP-ribose polymerase [PARP] inhibitors) targeting single-stranded DNA repair while homologous recombination in BRCA-mutant tumors or BRCA tumors is defective. Many studies have tried to find a homologous recombination deficiency (HRD) biomarker with the goal of better predicting PARP inhibitors and DNA-damaging chemotherapy responders (Timms *et al.*, 2014).

The potential role of PARP inhibitors in TNBC

Based on the idea of synthetic lethality, PARP inhibitors have been constructed to treat cancers with particular DNA-repair deficits, like TNBC with BRCA1/2 symptoms such as fatigue, hot flashes, limb edema and elevations of transaminase. A second survey assessed the activity of the next-generation antiandrogen enzalutamide in advanced AR-positive TNBC. This study was a two-stage, multicenter Phase II trial. In stage 1, 26 patients were assessed at 16 weeks for the primary end point of the CBR. Such patients did receive oral dose of 160 mg of enzalutamide per day. The result of stage 1 was 42 percent CBR16, including one CR and one PR.71 165 patients were screened for stage 2 study and 75 patients had 10 percent AR IHC and more than one post baseline assessment.TNBC patients had a one-line mean of lifetime therapy. The findings were presented at the 2015 meeting of the American Society of Clinical Oncology and showed a 35 percent CBR16 and a 14.7-week median PFS. Because of these results, interest in androgen blockade therapy is growing in the LAR subtype. Obstructing the AR pathway is a promising way to treat metastatic patients with TNBC's LAR subtype. While this new targeted therapy is promising, more data are needed before it can be considered a new validated option for treatment (Traina *et al.*, 2015).

Potent Nano carriers for targeting TNBC

Nanotechnology is a scientific development field with potential for the imaging, control, diagnosis and delivery of chemotherapeutic drugs to tumor site. NPs deliver drugs with improved effectiveness and decreased toxicity, and are capable of overcoming biological obstacles, thereby increasing the function of anticancer. Nano-medicine is now a developing approach that increases its therapeutic efficacy to deliver the medication.It plays an important role in the advancement of nanomedicine in breast cancer management

Carbon nano-materials associated carrier

Because of their biocompatibility, flexible chemical functionalization, effective drug delivery strategy and robust physio-chemical properties, carbon nanomaterials such as carbon nano-tubes, fullerenes, and graphenes have been the subject of interest for researchers. Recent reports have shown that these materials can be used for the therapeutic agents controlled drug delivery and also as contrast agents for the diagnosis, imaging and location of tumours. Fullerenes, CNTs and graphenes can be used on the surface to diagnose and treat cancer with imaging agents and chemotherapy. Using a non-invasive technique that could also kill tumor cells by combining photodynamic and photothermal effects, formulated carboxyl functionalized graphene revealed as a possible imaging agent of tumors in deep tissue.There are excellent fluorescence properties of amine-functionalized fullerenol nanocarrier which also have the ability to easily penetrate in vitro BC cells (MCF-7).The PEG-GO nanosheets that contain SN38, a camptothecin analog, are soluble in aqueous solvents. This nano-carrier exhibits anticancer effect in aqueous solvents with improved biocompatibility and increased stability. There were anti-proliferative effects on cancer cells such as MDA-MB-436, SK-BR-3, MDA-MB-231 and MCF-10A in vitro nano-sheet studies. Researchers suggested that nano-sheets of PEG-GO altered the oxidative phosphorylation of BC cells in mitochondria, without affecting normal cells. A labeling technique used to understand the mechanism of PEG-modified graphene oxide nano-sheets on both BC cells and healthy cells is called SILAC (Stable Isotope Labeling by Amino Acids in Cell Culture) which quantifies the protein's expression.PEG-GO specifically down-regulated PGC-1a protein expression in tumor resulting in the modification of proteins involved in energy generation by inhibiting oxidative phosphorylation in mitochondria causing alteration in the F-actin cytoskeleton assembly and decreasing the synthesis of ATPs. Suppression of ATP synthesis can inhibit invasion and metastasis of cancer cells (Zhou *et al.*, 2014).

Bismuth lipophilic Nanoparticles

Bismuth is considered as "green" element, as well as the pnictogen group's heaviest member. Given no direct application of bismuth to breast cancer cells, it was discovered that bismuth loaded compounds such as thiosemicarbazone, hydrazone, and dithiocarbamate portrayed potent anticancer activity. Research on the Bi (III) hydrazine compound was tested against MCF-7 cell lines and the outcome of the in vitro evaluation indicated that these cancer cell lines are successful. The Bismuth lipophilic nanoparticles (BisBAL NPs) have

been tested against the cell line of human breast carcinoma MCF-7 in another study. These NPs induced dose-dependent tumor growth inhibition, and growth inhibition at 1μM in MCF-7 cells was reported to be 51 per cent. The process that involves loss of plasma membrane integrity and genotoxic impact on genomic DNA also triggers the cell apoptosis. It's an innovative nanomedicine treatment for cancer (Hernandez-Delgadillo *et al.*, 2018).

Multifunctional core-shell nanomedicine

The multipurpose core-shell nanomedicines has the potential to prevent tumor metastasis through photodynamic action with increased cytotoxicity. Production of core-shell nanomedicine consisting of PLGA nanocore encapsulating m-tetra (hydroxyphenyl) chlorine (mTHPC) as a photo-sensitizer and albumin nanoshell containing Dasatanib (a 20 nm particle diameter tyrosine kinase inhibitor). The MDA-MB-231 in vitro studies demonstrated the disruption of Src kinase protein involved in metastatic cancer cell migration. The combinatorial delivery of Dasatinib with mTHPC in PLGA nano core produced the synergestic cytotoxicity in both MDA-MB-231 metastatic cell and MCF-7 (non-metastaic tumor cell) by the photoactivated oxidative stress mechanism. Using the photosensitizer, this leads to Src inhibition, which in turn causes apoptosis in metastatic cancer cells. The use of nanomedicine as photodynamic killing is an emerging strategy against TNBC.

Therapy with mesoporous silica nanoparticles (MSNs)

A mixture of medications is mainly intended for patients with cancer when the tumor cells defeat the drugs. To address this weakness associated with other delivery carriers, the mesoporous silica nanoparticles (MSNs) are used as an emerging nanocarrier.MSN co-administration of DOX and siRNA was more successful in inhibiting tumor growth in vivo and also generated synergistic effects compared to native drug treatment alone and siRNA treatment. The MSNs show competent intracellular defense due to the narrow distribution of pore size.The adsorption and release of siRNA may be altered by altering the siRNA coating. Since it is difficult to load into the heart, SiRNA is adsorbed onto the surface of NPs and modified catatonically. MSNs are covered with a coating of polyethylene imide (PEI), which is a gene transfection agent. Particles or nucleic acids in the 10-100 ratio were observed to demonstrate site-specific distribution and efficient adsorption.The modification of the siRNA surface using organophosphate is not as efficient as PEI. But these approaches are only useful for observation in vitro.The bulk of siRNA absorbed is rapidly lost when given in vivo due to the presence of nucleases in the plasma.To prevent this, loading state optimization is done along with the use of MSNs consisting of larger pores.Scientists have made several attempts to create MSNs such as larger pores of size ranging from 10 to 24 nm or using large numbers of amino groups to immobilize and enhance siRNA interactions in them.This also enhances the diffusion time of mesoporous activated siRNA or cytotoxic products. Externally coated MSNs with a layer of lipid or polyethylene glycol make them ideal carriers for successful treatment of cancer (Darvishi *et al.*, 2017).

Drug Targeting to molecular level in TNBC

Inhibition of TNBC metastasis requires therapeutic targeting to the level of the molecules. The molecular therapy varies the activity of programmed over-expressed receptors, proteins, hormones or changes the mechanisms for DNA repair. Several molecular therapies were available to treat TNBC with greater selectivity and efficacy such as PARP inhibitors, EGFR inhibitors, and VEGF inhibitors.

Inhibitors of poly (ADP-ribose) polymerase (PARP) have shown an increased, synergetic advantage in chemotherapy.PARP tends to help to repair DNA breaks in single strands. The mutant genes of the germline BRCA1/BRCA2 act as tumor suppressor proteins which repair DNA breaks in double strand.PARP inhibitors block the process of DNA repair in tumor cells thereby causing damage to DNA and interrupt the DNA replication fork to stop DNA replication.PARP inhibitors such as Olaparib, Talazoparib have shown improved clinical impact in TNBC patients and are being investigated in phase III clinical trials. In the same way, Veliparib is being studied in phase III in conjunction with carboplatin and PTX. In TNBC patients, PARP inhibitors administered with immunotherapy showed better clinical efficacy to inhibit BRCA1/BRCA2 mutant genes and DNA repairs in germline. It also described extended survival and improved quality of life for patients with BC.

The higher clinical benefits of BC have been indicated by anti-angiogenic agents such as Bevacizumab in conjunction with first-line chemotherapy such as PTX and DTX. Bevacizumab is an Anti-VEGF-A monoclonal antibody that suppresses angiogenesis. Unfortunately, no clinical evidence for predicting benefit on TNBC has been available. Bevacizumab however is being tested for TNBC diagnosis.

In TNBC, it is found that 70 percent of the population over-expresses the EGFR. This over-expression

is associated with poor tumor prognosis, and avoids traditional chemotherapy as well. Chemotherapeutic administration combined with EGFR inhibitors creates synergistic effect. For instance, Cetuximab, a monoclonal anti-EGFR antibody in combined effect with carboplatin, showed overall response rate of 17 percent with clinical benefits of 10 percent over the population, which is higher than the single treatment of Cetuximab or carboplatin showing clinical benefits of 6 percent. However, limited assessments have been made of the research on molecular targeting using these molecular therapies in combination with traditional chemotherapeutics through nanomedicine delivery. Even so targeted NPs have been explored earlier for the delivery of peptide, aptamers, miRNA, and siRNA. The nanocarrier-based delivery of therapeutic agents for the TNBC treatments is therefore of interest to the researchers (Kydd *et al.*, 2017).

CONCLUSIONS

The further treatment of TNBC remains as an important challenge. Some other data shows positive outcome in platinum based chemotherapy, PARP inhibitors and AR inhibitors.

Nano-medicine helps to make significant progress in the diagnosis as well as treatment of toxic hormones. Carbon nano-materials as well as novel therapeutic agents can be used as diagnostic. Also used for targeted therapy are mesoporous silica nano particles which have revolutionized the drug delivery field. Various other forms of therapeutic agents identified as the TNBC's potent inhibitor. However, literature does not consider such agents to be investigated as nanomedicinal products.

We need to change the manner in which we handle TNBC over the long term, so we view it as a chronic illness.Implementation of it will only come about through a willingness to identify and redefine a given tumor's molecular signature at multiple points along its evolutionary lineage so that therapy can be adapted to an evolving tumor microenvironment.

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