Review Article

Hacettepe University Journal of the Faculty of Pharmacy
Volume 43 / Number 2 / June 2023 / pp. 174-184

Novel Treatment Strategies for Triple-Negative Breast Cancers: A Comprehensive Review

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Received date :07.04.2022
Accepted date : 10.04.2023

DOI: 10.52794/hujpharm.1099683

ABSTRACT

Breast cancer has remained a serious health concern globally for women despite the healthcare advances which have enabled early diagnosis and treatment. Due to its metastatic ability and development of resistance to chemotherapies, triple-negative breast cancer is an extremely challenging subtype to treat. Targeted and optimized therapy is imperative as these tumors have higher recurrence rates than other types of breast cancers. This review is focused on the novel therapeutic strategies that have been proposed for the treatment of these aggressive cancers including alternative approaches like patient selection using biomarkers, metabolic reprogramming and development of smart drug delivery systems (SDDS) using targeted nanoparticles to treat the tumors as well as ensure prevention of recurrence. All of these approaches are aimed towards removing and treating the malignancies of triple-negative breast cancer (TNBC) and optimizing the therapies according to the patient cohorts. Further research is, however, necessary for the designing of an effective therapeutic regimen for patient sub-groups suffering from TNBC.

Keywords: Triple-negative breast cancers, Metabolic reprogramming, Biomarkers, Nanoparticles, Smart drug delivery systems

1. Introduction

In the year 2020, 2.3 million women were diagnosed with breast cancer and almost 685,000 fatalities occurred across the globe. In 2021, breast cancer is the world's most prevalent type of cancer making it a global public health concern [1,2]. It occurs in almost all countries in the world in women at any age post-puberty, however, the susceptibility increases with increasing age. Although certain etiological factors may increase the risk of developing breast cancer, nearly half of the total cases occur in females who have no risk factors other than gender and age [3]. The female gender is primarily the most significant etiological factor for breast cancer and only 0.5-1% of the total cancer cases occur in men [2]. Breast cancer can be broadly classified into 3 major subtypes based on molecular markers for human epidermal growth factor 2 (HER2) i.e. v-erb-b2 avian erythroblastic leukemia viral oncogene homolog 2 (ERBB2); formerly known as HER2 and estrogen or progesterone receptors: triple-negative (the tumors which lack all three of the standard molecular markers; 15%), ERBB2 positive (15%-20%), hormone receptor-positive/human epidermal growth factor 2 negative ERBB2 negative (70% of patients) [4,5]. Many cases are non-metastatic at early stages where the main focus of treatment outcome is simply the eradication of tumor and prevention of recurrences. Certain breast cancers progress from hormone-dependent tumors to hormone-independent diseases thereby limiting the therapeutic efficacy of nontoxic hormonal therapies as the hormone-independent tumors lack sensitivity towards hormone treatments [1]. The critical issue concerning these tumors is the alterations that occur within cancerous cells to modify their response to endocrine therapies [6].

2. Material and Methods

Data were extracted from various clinical, pathological, laboratory, and chemotherapy information published in different journals. Literature between year 1989 and 2022 was scanned. Keywords such as triple-negative breast cancers; metabolic reprogramming; biomarkers; nanoparticles; smart drug delivery systems based upon the pathophysiology, diagnosis and treatment strategies of triple negative breast cancers.

2.1. Introduction to Triple-negative breast cancer:

Triple-negative breast cancers are those which lack expression of ERBB2, receptors for estrogen and progesterone [7,8]. The two most commonly used ERBB2-negativity definitions include the tumors having immuno-histochemical scores of 0/1+ or tumors with scores of 0/1+ or 2+ that lack ERBB2 gene amplification after hybridization has been carried out in situ [9]. Basal-like cancers are part of the subgroups of cancers where there is minimal or absence of estrogen receptors and a distinct absence of ERBB2 over expression. Many cancers can be characterized under both basal-like and TNBC subtypes [10,11]. Since both basal-like and triple-negative breast cancers have resemblances in terms of their phenotypic expression, these are effectively used synonymously [12,13]. Triple-negative cancers also include other molecular subtypes such as claudin-low and interferon-rich subgroups as well as the normal-breast-like subgroup. The claudin-low tumors are distinctive for the presence of cells that have properties similar to those of stem cells and epithelial-to-mesenchymal transitions features. The interferon-rich subtype tends to be easier to predict with its disease prognosis than the other triple-negative breast cancers whereas normal-breast-like cancer shows an extremely high number of both normal and stromal cells [14,15]. In a research, non-metastatic TNBC from 2013 to 2019 were analysed for demographics, treatment trends, and survival using the Kaplan Meir technique. After a check for collinearity among the variables, prognostic factors for OS and DFS were assessed using the Cox Proportional Hazard model estimator for univariate and multivariable analysis. The findings revealed that median disease-free (DFS) was 92.2 months at a median follow-up of 54 months, and overall survival (OS) was not attained. DFS and OS were predicted to be 65.9% and 80.3% during the next five years, respectively. There were 259 (20.0%) failures, mostly distant (204, 15.7%), with the liver (31.8%) and the lung (51%). In a multivariate analysis, stage III illness (HR-4.89, p-0.027), PNE (HR-2.09, p-0.003), older age (HR-1.03, p-0.002), and the presence of LVI (HR-2.00, p-0.003) were all linked to a worse overall survival rate [15].

2.2. Epidemiology of TNBC:

BRCA1 is a significant susceptibility gene and in >75% of breast cancers occurring in women carry-

ISSN: 2458 - 8806

ing a mutated BRAC1 gene show either a basal-like, a triple-negative or even both phenotypes [7,13,14]. Moreover, women belonging to lower socio-economic groups and belonging to African or Hispanic ancestry have a higher susceptibility towards this disease [8,16].

TNBC shows high genomic heterogeneity including multiple entities which show pronounced histopathological and transcriptomic characteristics. In addition to the transcriptional heterogeneity, TNBC shows high genetic instability as well as intricate patterns of rearrangements in the chromosome and copy number alterations. Certain distinctive characteristics seen in this type include poor tumor differentiation, medullary features as well as a stromal lymphocytic response.[17-19] It is a very invasive type of tumor which leads to nearly 46% of patients having distant metastasis occurring mostly in the third year after the disease has been diagnosed.[12] The molecular pathophysiology, however, requires further investigation.

2.3 Treatment:

Since HER2 amplification and estrogen and progesterone receptor expression are absent, the drugs acting on these three receptors are not useful in the treatment of TNBC [20]. Chemotherapeutic drugs are the only therapeutic agents which have been approved by the FDA Food and Drug Administration for the treatment of nonmetastatic triple-negative breast cancer. Although chemotherapy has shown significantly improved therapeutic outcomes, there is minimal reduction in the rates of recurrence of tumor growth. In certain cases, TNBC tumors develop resistance to chemotherapeutic agents making it imperative to design targeted adjuvant therapies for the treatment [21].

2.3.1. Targeted therapeutic regimens for the treatment of TNBC subtypes:

In the year 2011, six distinct subtypes were distinguished. by performing profiling of genotypic expression of 587 TNBC patients: immunomodulatory (IM), luminal androgen receptor (LAR), basal-like 1 (BL1), basal-like 2 (BL2), mesenchymal (M) and mesenchymal stem-like (MSL) [22,23]. This classification and profiling of TNBC is an important step in optimizing the treatment prescribed for each subtype to improve overall therapeutic outcomes. In the case of BL1 cancers, potential therapeutic agents are of poly (ADP-ribose) polymerase enzymes inhibitors (PARP inhibitors) and genotoxic agents. Poly (ADP-ribose) polymerase is a class of DNA repair enzymes having the major function of maintaining genomic stability, repairing DNA as well as participating in the progression of the cell cycle and eventually apoptosis [24,25]. These enzymes, if inhibited, will lead to the inability to repair DNA damage and cause cell death achieving the desired outcome. PARP inhibitors are proposed as targeted treatments of TNBC cases having mutations on the breast cancer gene-1 (BRCA1) but the clinical trials have not shown considerable efficacy [26,27]. Moreover, PARP inhibitors can tangibly improve the therapeutic outcomes which can be achieved by using radiation therapy and chemotherapeutic agents [28]. Based on two phase III trials that shown an improvement in progression-free survival when compared to chemotherapy, two PARP inhibitors i.e. olaparib and talazoparib have currently been licenced for the treatment of triple negative metastatic breast cancer. With supportive therapy, dosage pauses, and dose reductions, the safety profile was tolerable. talazoparib, rucaparib, and veliparib are three more PARP inhibitors that are now being researched. The probable future function of PARP inhibitors will then be explored [26-28]. Patients having BL1 type have also shown sensitivity to treatments with cisplatin. The mTOR inhibitors and inhibitors of human growth factors (cetuximab, lapatinib and gefitinib) are potential targeted treatments in BL2 subtypes [29].

The mesenchymal subtype, also called as metaplastic breast cancer, has a higher tendency to develop chemotherapeutic resistance. It shows signaling pathways related to cell migration, differentiation pathways and interaction pathways of extracellular matrix receptors were highly activated. Treatment of this subtype mainly includes mTOR inhibitors or the drugs which specifically target the epithelial-mesenchymal transition [30,31].

In the immunomodulatory breast cancer subtype, the main focus of treatment strategies is the inhibition of immune signaling. This subtype shows great similarity to medullary breast carcinomas [32]. The immunomodulatory subtype possesses signal transduction pathways as well as highly enriched immune cell-associated genes. The drugs that could potentially be employed for the treatment of these IM cancers are inhibitors of immune checkpoints (Ipilimumab,

Nivolumab), inhibitors of PARP and cytostatics such as cisplatin, carboplatin, satraplatin, lobaplatin, mercaptopurine, etc [33,34].

The treatment of MSL subtype of breast cancers, which show relatively lesser genes related to cell proliferation and more genes related to stemness, could include PI3K inhibitors, antiangiogenic drugs to prevent angiogenesis and Src antagonists [35].

The luminal androgen receptor subtype has a distinctive genomic expression than the other subtypes of TNBC tumors. This subtype does not show estrogen receptors but it does act through a highly activated hormone-related signaling pathway which includes metabolism of porphyrin, synthesis of steroids and metabolism of estrogen or androgen. It is important to note here that the androgen receptor is greatly expressed in the luminal androgen receptor subtypes and hence it is considered AR-positive. Hence, the recommended treatment strategy includes anti-AR therapy. The level of mRNA is observed to be nearly nine times the other subtypes [36].

It has been concluded by performing prognostic analyses of the six TNBC subtypes that the LAR subtype has a greater distant metastasis-free chance of survival as well as the overall rate of survival (OS), as compared to M and BL2 subtypes [37]. The BL2 and M subtypes have significantly higher recurrence rates post three years than those of LAR subtype of breast cancer. Treatment strategies of LAR subtypes focus on inhibition of AR signaling, ERBB4 and FOXA1signaling. Non-steroidal androgens, mTOR inhibitors and PI3K inhibitors can be potential targeted treatments for the LAR subtype. The proliferation of MDA-MB-453, which is the cell-line involved in LAR sub-type, can be inhibited by AR antagonists such as flutamide. Therefore, this could be proposed as a targeted regimen for the treatment of LAR-subtype patients through AR blockage [38,39].

2.3.2. Platinum compounds:

The cis-structured platinum compound, cisplatin, can have an inhibitory effect on tumor cells [33]. Research studies are currently aiming to assess the therapeutic response and efficacy of using platinum agents such as carboplatin and cisplatin to treat TNBC. The dysfunctional BRCA1 gene and its pathway is directly linked to a defect in the process of DNA repair which can lead to the sensitization of cells to therapeutic agents in animal models. [40,41] As loss in DNA repair is considered as a hallmark of certain triple-negative cancers, DNA-crosslinking platinum chemotherapies show potential as targeted therapeutic alternatives [42]. In triple-negative tumors which have been treated with neoadjuvant chemotherapeutic agents, pathologic complete response pCR (entailing that all tumors are removed from the breast and lymph nodes) after surgery is considered to be a very favorable prognostic biomarker. It was found that the addition of carboplatin to conventional chemotherapy including taxel and anthracycline leads to a significant increase in the pCR rate in patients, but the same isn't replicated in HER2- positive patients [43]. In two randomized trials carried out to assess the therapeutic efficacy of neoadjuvant therapies with or without carboplatin, both treatments showed improved pathologic complete response (pCR) but only one of them showed a considerable increase in the disease-free survival rates in the carboplatin group. The other components of the chemotherapeutic regimen in this particular case were not kept consistent with standardized conventional therapy and also did not administer an alkylating agent [44,45].

2.3.3. Pembrolizumab:

It has been concluded through phase 3 trial that in cases of early TNBC, the total percentage of individuals showing pCR was significantly higher in the patients who were treated with pembrolizumab in addition to neoadjuvant treatment than among those who received placebo in combination with the neoadjuvant treatment. It was observed in this study that the benefits of pembrolizumab in terms of the pathological complete response remained generally consistent throughout the sub-groups, including the groups showing programmed death ligand-1 (PD-L1) expression [46].

2.3.4. Salience of Patient-selection for the treatment of TNBC:

Although there has been extensive research carried out to identify chemotherapeutic agents which remain to be the fundamental backbone of the treatment strategy for the treatment of TNBC, only a few of the drugs transition to clinical practice. Multiple clinical trials have illustrated that pre-selecting patients based on specific biomarkers may be extremely beneficial for designing targeted therapy [47,48]. Employing and validating biomarkers in the clinical

ISSN: 2458 - 8806

management of TNBC in the future is evidenced by these studies [49]. Recently, the first trial results in TNBC were published which would make it possible to accurately stratify the patients having tumor gene signatures [50]. There have been many studies conducted on a large scale to identify newer targets which also include shRNA/CRISPR screens [51-53]. It is anticipated that the clinical sequencing which has been carried out across various institutions will be standardized and implementation of machine-learning (ML) based models will aid in optimizing the extraction of clinical data from electronic medical documentation which will allow effective integration of both clinical and genomic information [54].

2.4. Metabolic reprogramming:

Since there are many limitations in the options available for the treatment of triple-negative disease and the risk of drug- resistance, it is essential to employ targeted and optimized novel treatment strategies for TNBC. Since metastasis is a major contributing factor in cases of fatalities in TNBC, metabolic reprogramming could act as a significant treatment strategy for metastatic tumors as these adapt to their distinctive microenvironments at their secondary sites. Further research regarding molecular reprogramming is necessary to identify appropriate therapeutic targets [55].

German physiologist, Otto Warburg identified the fundamentals of the major metabolic reprogramming which can be done in cancerous growths. He proved that the cancerous cells maintain their ATP levels by increasing the levels of glycolytic reactions, regardless of the availability of oxygen, known as the Warburg effect [56,57]. However, in TNBC tumors both glycolysis and oxidative phosphorylation (OXPHOS) can be observed [58]. The metabolic profiles of these tumors are very distinctive according to their site-selective metastasis. It can be observed that the liver metastatic tumors produce energy through glycolysis but bone and lung metastases rely predominantly on OXPHOS [59].

It has been concluded that FAO is a prominent metabolic program that increases the chances of survival of the metastatic TNBC cells. Elevated FAO levels inherently limit the toxicity caused by oxidative stress, which, in turn, benefits the survival of the cancer cells in the pro-oxidative lung region. Inhibiting the dimerization of CDCP1 in TNBC cells by causing expression of the released component of cleaved CDCP1 shows a significant reduction in the abundance of LD and could reduce metastatic ability tangibly in these cells. Thus, blocking oxidative phosphorylation of OXPHOS and CDCP1-driven FAO may cause inhibition of TNBC metastasis [60].

Chemoresistance is also a major cause of TNBC patient mortality making it crucial to combat this resistance using concurrent therapies. It is observed that Chemo-resistant TNBC cells tend to show increased glycolysis along with increased uptake of glucose and lactate fermentation [61]. Silencing and inhibiting the enzymes which act within aerobic glycolysis could help in enhancing the anti-proliferation activity shown by chemotherapeutic agents. Since fatty acids are major mediators of chemoresistance of tumors, FAO inhibitors may help to sensitize the chemo-resistant TNBC cancerous cells to chemotherapeutic drugs [62].

In the TNBC cells showing chemo-resistance, paclitaxel-based therapeutic regimen leads to endoplasmic reticulum stress and also is responsible for promoting the interaction between human SLC1A5 transporter and ring finger protein 5 (RNF5). Consequently, human SLC1A5 undergoes ubiquitination modification as well as degradation, which will further lead to impairment in the uptake of glucose, retarded TNBC cancerous growth as well as decreased mTOR activity. In addition to this, inhibition of RNF5 also induces resistance to paclitaxel therapy. Positive prognosis in these cases is often linked to low SLC1A5 expression and High RNF5 expression. Phosphoglycerate dehydrogenase (PHGDH) plays a vital role in the metabolism of serine and is also involved in the sensitization of the triple-negative cancerous cells towards the drugs administered. If the Phosphoglycerate dehydrogenase deficient cells are treated with either doxorubicin or carboplatin at IC50 concentration respectively, an elevation of mitochondrial reactive oxygen species ROS and increased apoptosis is observed [63].

3. Potential nano-systems for the treatment of TNBC:

Nanoparticles are now at the frontier of novel targeted drug delivery systems having major potential in the treatment of cancers. Enhanced permeability

and retention (EPR) effect also increases the payload drug retained at the site of action and thereby targets the tumor site without damaging the normal non-malignant tissue. Stimuli-responsive nanoparticles could be utilized in treating TNBC as they show site-specific drug transport, longer drug retention at the site of the tumor as well as minimized drug distribution at off-target sites [64]. These smart nanoparticles respond to certain tumor-specific stimuli such as lower pH (around 6.5), hypoxic conditions, reactive oxygen species ROS as well as excessive enzyme production. The raised temperature of tumors is also a stimulus that can be utilized to control drug release and is being evaluated for smart drug delivery systems *in vitro* and *in vivo* [65,66]. The stimuli-responsive ability aids in enhancing target selectivity of the delivery systems, thereby decreasing the total dose required to achieve therapeutic outcomes and also preventing damage to healthy normal cells. The antitumor efficacy of the therapeutic regimen could be drastically improved using smart drug delivery systems (SDDS). The theragnostic approach offered by nanoparticles can essentially transform therapy for TNBC wherein multifunctional nanoparticles act as both drug delivery systems as well as facilitate imaging of the tumor to assess the response to treatment. This will enable physicians to accurately analyze the therapeutic efficacy of the drugs and optimize the treatment accordingly [67].

3.1. Liposomal nanoparticles:

Liposomes are nanoparticle drug carriers that possess a phospholipid bilayer around a spherical vesicle. Research regarding non-targeted liposomes has been carried out to facilitate TNBC treatment [68]. Furthermore, imaging of the tumor progression can be done using imaging agents such as magnetic iron oxide nanoparticles, radioisotopes and organic dyes which are either encapsulated within the liposomal bilayer or complexed with the liposome directly. This, in turn, will help increase the drug concentration inside the cancerous cells and allow imaging of the tumor to monitor the drug delivery as well as treatment response. A paclitaxel formulation Endo-Tag-1 has also been validated for the treatment of advanced triple-negative cancer. The cationic liposome which contains paclitaxel drug is attracted to the tumor site which is negatively charged leading to targeted drug delivery [69].

3.2. Gold nanoparticles:

These metallic nanoparticles have been designed for imaging, thermal treatment as well as for delivery of drugs to cancerous cells. Gold nanoparticles also possess the ability to absorb incident light at certain specific wavelengths and generate heat which can be used for photothermal cancer therapy. Another nanosystem that was studied showed absorption of plasmon in the near infra-red region and photothermal coupling ability [70]. Photothermal ablation therapy through gold nanorods could be hence further explored for the treatment of TNBC. Multilayered gold nano-systems ($Au/SiO_2/Au$) have a gold shell covering on the outside and a gold core encapsulated within silica on the inside. Systemic administration of a multilayered gold nanoparticle along with irradiation therapy tangibly inhibited the growth of the tumors and effectively removed the tumors in certain mice for more than 60 days as well [71]. A major limitation that must be tackled before the development of gold nano-systems is enabling the degradation and elimination of these nanoparticles outside the body to prevent any toxic side effects [72].

3.3. Silver nanoparticles (AgNPs):

Silver nanoparticles could potentially treat aggressive triple-negative cancers as they have shown efficacy in preclinical disease models. These nanoparticles cause selective damage to DNA and depletion of cellular antioxidants in triple-negative tumors but not to the normal breast cells observed in 3D cell cultures [64]. Both TNBC cells and normal non-malignant breast cells are equally sensitive to silver cations, hence it is necessary to formulate them as nanoparticle systems to ensure targeting of TNBC tumor cells only [73,56]. Another study concluded that exposure to silver nanoparticles can be linked to increased proteotoxic stress and apoptosis which could essentially be used to selectively treat the claudin-low subtype of TNBC. The concentration which was found to be lethal for claudin-low cancers was additionally proved to be entirely non-toxic to non-malignant breast epithelial cells providing targeted treatment [74].

3.4. Magnetic iron oxide nanoparticles:

Magnetic iron oxide nanoparticles (IONP) act as excellent theragnostic agents as they can act as drug delivery systems in addition to MRI contrast im-

ISSN: 2458 - 8806

aging agents. These nanoparticles have distinctive paramagnetic properties and are safe for clinical applications in humans as they are biodegradable with lesser toxic effects. These can be used widely as imaging probes as MRI offers complete tissue penetration, thorough imaging of soft tissues and greater 3D resolution of the tissue anatomy. In a 4T1 mouse model for breast cancer, IONP was validated as a targeted therapeutic agent as well as the MRI property enabled assessment of drug delivery to cancer site [75]. The nanoparticles which can specifically target under-glycosylated Mucin 1 (MUC-1) were developed for the main function of monitoring the treatment response of cancer cells to Dox in the human triple-negative cancer model. In human breast cancer and other malignancies, mucin 1 (MUC1), a heterodimeric protein made of two subunits, is abnormally over expressed. In the past, the shed mucin component was the main focus of most of the early research on MUC1.[76] Nevertheless, more recent research has focused on the oncoprotein known as the transmembrane MUC1-C-terminal subunit (MUC1-C). The PI3K to AKT and mitogen-activated protein kinase (MEK) to extracellular signal-regulated kinase (ERK) pathways are both activated as a result of MUC1-C's interactions with EGFR (epidermal growth factor receptor), ErbB2, and other receptor tyrosine kinases at the cell membrane. Moreover, MUC1-C localises to the nucleus, where it stimulates the Wnt/β-catenin, STAT, and NF (nuclear factor)-B RelA pathways.[77] These results and the proof that MUC1-C is a druggable target have given researchers the experimental foundation for creating drugs that interfere with MUC1-C function. Importantly, MUC1-C subunit inhibitors have been created, directly blocking its oncogenic action and causing the death of breast cancer cells in culture and in xenograft models. These results led to the phase I assessment of a first-in-class MUC1-C inhibitor as a possible therapy for patients with breast tumors who express this oncoprotein [78].

3.5. Clinical studies evaluating new treatment options

Early-stage (I-III) TNBC patients can still benefit from chemotherapy that includes anthracyclines, taxanes, and antimetabolites. Even with the inclusion of a poly (ADP-ribose) polymerase (PARP) inhibitor, platinum-based treatments have been demonstrated to increase the overall pathologic complete response (pCR), but there is inconsistent information about their impact to disease-free survival (DFS) and overall survival (OS). When given adjuvant capecitabine treatment, patients with residual illness following neoadjuvant chemotherapy and surgical surgery had a substantial increase in overall survival [79]. Because of the substantial mutation load in metastatic TNBC (mTNBC), immune checkpoint inhibitors and targeted treatments are possible. If a monoclonal antibody is added to the treatment regimen for mTNBCs that express PD-L1 receptors, responsiveness and survival may be enhanced. Regardless of the degree of biomarkers expressed by the tumor cells, antibody-drug conjugates (ADCs) can administer large doses of chemotherapy and dramatically affect survival in mTNBC [77]. When used on newly diagnosed, treatment-naive mTNBC patients, PARP inhibitors greatly increase survival, but they have had mixed effects when used on patients who have previously received therapy. The use of PARP inhibitors might give patients with somatic breast cancer (BRCA) and partner and localizer of BRCA-2 (PALB2) mutations greater treatment choices. The future of treatment may lay in anti-androgen therapy or the creation of cancer vaccines that might boost the immunogenicity of the tumor environment, whereas other uncommon targets have had conflicting outcomes [78].

4. Conclusion

Due to its high genomic heterogeneity, aggressive metastatic ability and tendency to develop chemotherapeutic resistance, Tumor negative breast cancer poses a critical challenge to healthcare professionals. Over the past decade, extensive research in therapies targeting these tumors has made it possible to classify them into subtypes and employ combinatorial therapeutic regimens to treat them effectively. In addition to this, patient selection and precise stratification using biomarker-driven integrated data have been proposed to be an excellent solution to this exacerbating problem. Nanoparticles provide a dual-action of diagnosis along with the therapeutic drug delivery which is targeted to specific tumor tissues and offers higher retention through enhanced permeability and retention effect. Treatment of TNBC, going forward, would be a multi-layered approach utilizing metabolic reprogramming, patient selection and novel targeted chemotherapeutic agents to ensure pathological complete response and also prevent recurrence of TNBC tumors.

Acknowledgements

Authors are grateful to the management of School of Health Sciences and Technology, Dr. Vishwanath Karad, MIT World Peace University, Kothrud, Pune for giving support and motivation for writing this review.

Conflict of Interest

Authors declare no conflict of interest

Statement of Contribution of Researchers

Concept – J.N., B.K., A.K., R.P.; Design – J.N., B.K., A.K., R.P.; Supervision – B.K.; Resources J.N., A.K., R.P.; Materials – J.N., B.K., A.K., R.P.; Data Collection and/or Processing – J.N., B.K., A.K., R.P.; Analysis and/or Interpretation – J.N., B.K., A.K., R.P..; Literature Search – J.N., A.K., R.P.; Writing – J.N., B.K., A.K., R.P.; Critical Reviews – B.K., A.K., R.P.

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ISSN: 2458 - 8806

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