Nano-based Drug Delivery System for Treating Triple-negative Breast Cancer (TNBC)

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Abstract. Triple-negative breast cancer (TNBC) is a highly aggressive subtype with limited treatment options, primarily due to the lack of hormone receptors and HER2 expression. Nano-based drug delivery systems, including PEGylated liposomes, polymeric nanoparticles, and gold nanoparticles, present a promising strategy to enhance therapeutic outcomes by improving drug solubility, targeting tumor cells more effectively, and reducing systemic toxicity. These nanoparticles utilize both passive and active targeting mechanisms to address TNBC's resistance to conventional therapies. This paper reviews the underlying mechanisms, challenges, and current clinical trials of nano-based drug delivery systems for TNBC treatment, emphasizing their role in improving treatment effectiveness and patient results.

Keywords: Breast cancer; Triple-negative breast cancer (TNBC); Nanoparticle; Drug delivery; Cancer treatment.

1. Introduction

The incidence of breast cancer (BC) has been continuously increasing on a global scale, making it the main cause of deaths related to cancer among women. In 2022, 2.3 million new cases of BC were reported globally, resulting in approximately 670,000 deaths [1]. For 2024, An estimated 310,720 new cases of invasive breast cancer, along with 56,500 cases of non-invasive breast cancer, are expected to be diagnosed in women across the U.S. BC has become the most frequently diagnosed cancer among women globally, making up approximately 30% of all newly reported cancer cases in females [2].

The development of BC is linked to a combination of genetic, hormonal, and environmental factors. Mutations such as BRCA1 and BRCA2 increase DNA instability and lead to cancer. Hormones such as estrogen drive cancer growth, particularly in hormone receptor-positive cancers [3]. The tumor microenvironment, such as immune and stromal cells, supports tumor growth and immune evasion. This complexity makes breast cancer highly variable in its progression and treatment.

Breast cancer involves a variety of diseases differentiated in receptor expression, histologic types, clinical characteristics and reactions to different therapies. In the last 15 years, breast cancers have been classified according to their expression of progesterone receptor (PR), estrogen receptor (ER) and anti-human epidermal growth factor receptor 2 (HER2) because of the effective treatments developed for subsets of breast cancer expressing these 3 receptors. The concept of triple-negative breast cancer (TNBC) was put forward in the mid-2000s, revealing its absence of expression of ER, PR and HER2 [3]. In the early 2000s, TNBC was initially confirmed as a clinical entity with the seminal gene expression microarray studies [4].

The triple-negative phenotypes are also displayed in over 85% of breast cancers which develop *BCAR1*germline mutations [3,4]. TNBC presents major challenges because of its aggressive nature and the lack of effective treatment options. Its absence of expression of ER, PR and HER2 precludes the use of hormone or targeted therapies. Additionally, TNBC is linked to an increased likelihood of early recurrence and distant metastasis, which adversely affects survival rates. Moreover, the presence of BRCA1 mutations in a subset of TNBC patients increases the risk of treatment resistance [3]. As a result, TNBC is considered one of the deadliest subtypes of breast cancer, highlighting the need to investigate new therapeutic approaches.

Considering the limitations of traditional treatments for TNBC, nanotechnology-based drug delivery systems offer a promising solution. Current nano-based drug delivery systems include a variety of platforms like PEGylated liposomes, polymeric nanoparticles, albumin-bound nanoparticles, gold nanoparticles, etc. These systems enhance drug bioavailability and selectively target tumor cells, reducing off-target effects and overcoming drug resistance. The continued investigation into nanomedicine can significantly revolutionize the treatment for TNBC by addressing its intrinsic therapeutic challenges.

2. Pathogenesis of TNBC

2.1. Characteristics of TNBC cells

TNBC cells are characterized by high levels of genomic instability, often manifesting as complex genomes with frequent mutations in key driver genes, particularly TP53, which is mutated in over 80% of cases [4]. Other recurrent genetic alterations include mutations in the PIK3CA and BRCA1 genes, the latter being significantly associated with the basal-like subtype of TNBC. BRCA1 germline mutations are present in 11% to 19% of TNBC patients, further highlighting the relationship between homologous recombination DNA repair deficiencies and this cancer subtype [3,4]. In addition to point mutations, TNBC cells frequently exhibit copy number alterations, including gains in chromosomal regions 1q, 8q, and 10q and losses in 5q and 8p [4].

TNBCs display a wide histological diversity, with some subtypes exhibiting distinct features such as squamous and spindle cell morphology, which are more common in metaplastic breast cancers, a TNBC subtype [4]. Metaplastic TNBCs are enriched in mutations affecting the PI3K and Wnt signaling pathways, in contrast to other TNBC subtypes, which often harbor TP53 mutations and alterations in DNA repair genes [5]. Another notable subtype is the apocrine carcinoma, which is associated with androgen receptor (AR) positivity and distinct genomic alterations, including mutations in PIK3CA, AKT1, and NF1 [6].

On a molecular level, TNBC has been further classified into multiple subtypes based on transcriptomic analyses. Basal-like subtypes exhibit elevated expression of genes which are linked to cell cycle control and DNA damage response, whereas the mesenchymal subtype is enriched with genes linked to cell motility and epithelial-mesenchymal transition (EMT) [4,5]. The luminal androgen receptor subtype, shows significant AR signaling activity and shares some molecular similarities with luminal breast cancers, including mutations in PIK3CA and GATA3 [6]. These molecular differences result in varying clinical outcomes and responses to therapy, making the identification of TNBC subtypes crucial for personalized treatment approaches.

2.2. Tumor microenvironment and immune response in TNBC

The tumor microenvironment (TME) is integral to the advancement and therapeutic resistance observed in TNBC. It is composed of a diverse array of non-cancerous cells, including fibroblasts, immune cells, endothelial cells, and extracellular matrix components, all of which engage in intricate interactions with TNBC cells to promote tumor growth, invasion, and metastasis. In TNBC, the TME is frequently more immunosuppressive than in other breast cancer subtypes, contributing to the aggressiveness of the disease and its resistance to standard treatments [4].

A prominent characteristic of the TNBC microenvironment is the infiltration of tumor-infiltrating lymphocytes (TILs), which can either facilitate or suppress tumor growth based on their composition and functional activity. Elevated levels of TILs, especially cytotoxic CD8+ T cells, are typically correlated with a more favorable prognosis and enhanced responses to treatments such as immune checkpoint inhibitors. However, many TNBCs display low levels of CD8+ T cells and a higher prevalence of immunosuppressive cells, which facilitate immune evasion [5]. Additionally, tumor-associated macrophages, especially the M2-polarized subtype, contribute to tumor growth, angiogenesis, and metastasis by releasing pro-tumorigenic cytokines and growth factors [4].

The stromal component of the TME in TNBC is also crucial in regulating immune responses. Cancer-associated fibroblasts are prevalent in the stroma of TNBC and play a role in immune suppression by releasing cytokines, including transforming growth factor-beta (TGF-β), which diminishes the activity of cytotoxic T cells and facilitates the recruitment of immunosuppressive cells [6]. Cancer-associated fibroblasts contribute to tumor invasion and metastasis by remodeling the extracellular matrix and promoting EMT in TNBC cells [4].

Beyond its role in immune suppression, the TNBC microenvironment is also highly vascularized, aiding in the spread of tumor cells to distant locations. TNBC cells, along with the TME, promote angiogenesis by elevating the levels of pro-angiogenic factors such as vascular endothelial growth factor (VEGF), which facilitates the establishment of new blood vessels vital for tumor progression and metastasis [3].

2.3. The involvement of breast cancer stem cells in the relapse of TNBC

Tumor relapse in both breast cancer and TNBC is driven by the pivotal role of breast cancer stem cells (BCSCs). The ability of BCSCs to self-renew and differentiate renders them resistant to conventional treatments such as chemotherapy and radiotherapy. This resistance enables BCSCs to survive treatment, contributing to minimal residual disease and leading to tumor relapse [7]. BCSCs exhibit drug resistance according to their quiescence, improved DNA repair capabilities, and upregulation of drug efflux transporters, such as ABCG2. In TNBC, BCSCs are enriched, correlating with its aggressive nature and high recurrence rates [8].

The tumor microenvironment provides a protective niche for BCSCs. Cancer-associated fibroblasts (CAFs) and hypoxic conditions within the TME promote BCSC survival and self-renewal through signaling pathways including Notch, Wnt and so on [9,10]. BCSCs are strongly associated with EMT, which increases their invasiveness and contributes to both metastasis and therapy resistance, particularly in TNBC [11].

New therapeutic approaches aim to target BCSC-specific pathways to prevent recurrence, with a focus on disrupting their supportive niche within the TME [12].

2.4. Challenges in treating TNBC

One of the primary challenges in treating TNBC is its high degree of resistance to chemotherapy. TNBC cells, particularly breast cancer stem cells (BCSCs), are adept at evading chemotherapy through various mechanisms, including elevated DNA repair efficiency and heightened production of drug efflux transporters like ABCG2 [3,9]. This resistance contributes to minimal residual disease following treatment, a key factor in TNBC’s high recurrence rate [8]. Furthermore, the plasticity of TNBC cells allows them to adapt to therapy, shifting between stem-like and differentiated states, which further complicates treatment [7].

The TME contributes greatly to TNBC’s treatment resistance. Components of the TME, including cancer-associated fibroblasts and immune cells, shield tumor cells from therapies by fostering a protective environment for both TNBC cells and BCSCs. Hypoxia within the TME enhances the stem-like characteristics of BCSCs through pathways like Notch and Wnt, increasing their survival and self-renewal capabilities, which contributes to recurrence and metastasis [10,11]. Moreover, the immune-suppressive nature of TNBC’s TME, with increased regulatory T cells and tumor-associated macrophages, reduces the effectiveness of immunotherapies and further complicates treatment strategies [8,9].

The absence of well-defined molecular targets in TNBC remains a significant obstacle in treatment. While targeted therapies such as hormone blockers and HER2 inhibitors have transformed the treatment landscape for other BC subtypes, TNBC lacks these actionable targets due to its receptor-negative status. As a result, growing research efforts are directed towards discovering novel therapeutic targets, including BCSCs and critical signaling pathways like Wnt/β-catenin and Notch, which play a role in the maintenance and survival of TNBC cells [12]. Nonetheless, targeted therapies for TNBC are still in the preliminary stages of development, and their clinical use remains restricted.

3. Nano-based treatment for triple-negative breast cancer

3.1. General mechanisms and signal pathways of nano-based treatment for TNBC

Nano-based treatments for TNBC primarily rely on improving drug delivery, increasing therapeutic efficacy, and reducing systemic toxicity. These mechanisms are made possible by utilizing the distinct characteristics of nanoparticles (NPs), such as their capacity to improve drug solubility, shield drugs from degradation, and direct them towards specific cells or tissues.

Passive targeting in nanomedicine is primarily driven by the foundational mechanism known as the Enhanced Permeability and Retention (EPR) effect. In tumors, including TNBC, the presence of leaky vasculature and dysfunctional lymphatic drainage allows nanoparticles to preferentially accumulate at the tumor site. By utilizing passive targeting, drug levels within the tumor are enhanced, while systemic exposure and associated toxicity are significantly decreased [13].

In addition to the passive EPR effect, many nano-based treatments employ active targeting strategies. Ligands such as antibodies, peptides, or small molecules can be attached to nanoparticles, allowing them to specifically target receptors overexpressed on TNBC cells, including EGFR and folate receptors. By binding to these specific receptors, active targeting enhances the uptake of nanoparticles by cancer cells and improves drug delivery [14].

TNBC tumors exhibit a more acidic microenvironment compared to normal tissues. pH-sensitive nanoparticles are engineered to release their drug payloads in response to the acidic environment, enabling the controlled release of chemotherapeutic agents specifically within the tumor. Similarly, certain nanoparticles are designed to react to tumor-specific enzymes, like matrix metalloproteinases (MMPs), which break down the nanoparticle shell and release the drug in a targeted manner within the tumor [13].

In TNBC, the PI3K/AKT/mTOR pathway is frequently altered, with a critical function in sustaining tumor cell survival and preventing apoptosis.Nano-based therapies, particularly those involving the co-delivery of PI3K inhibitors or mTOR inhibitors, aim to inhibit this pathway. By targeting and disrupting the PI3K/AKT/mTOR signaling cascade, TNBC cell proliferation can be effectively inhibited, and apoptosis can be induced using nanoparticles [15].

In TNBC, a critical role is played by the Wnt/β-catenin pathway, particularly in the regulation and maintenance of cancer stem cells (CSCs). Engineered nanoparticles designed to deliver inhibitors of this pathway have demonstrated potential in targeting CSCs, which are crucial in driving tumor recurrence and metastasis. By blocking the Wnt/β-catenin pathway, nanoparticle-based therapies can help reduce tumor aggressiveness and lower the risk of relapse [16].

TNBC tumors are known for their immunosuppressive TME, which hinders the efficacy of many conventional therapies. Agents that modulate the TME, like immune checkpoint inhibitors (e.g., anti-PD-1/PD-L1), can be delivered through specially designed nanoparticles, aiming to restore the immune system's capacity to identify and eliminate cancer cells. By targeting the TME, nanoparticles can improve the overall therapeutic outcome in TNBC treatment [17].

Many nanoparticles, such as gold nanoparticles (AuNPs), are employed in photothermal therapy (PTT), where laser-induced localized heating generates reactive oxygen species (ROS) within TNBC cells. The ROS disrupt cellular homeostasis, triggering cell death, while the heat produced during PTT amplifies tumor cell destruction by promoting apoptosis [18].

3.2. Nanoparticle modification for treating TNBC

3.2.1. Passive accumulation

3.2.1.1 PEGylated liposomes for Doxorubicin delivery

PEGylated liposomes are a well-established nanoparticle platform designed to leverage the EPR effect for passive accumulation in tumor tissues. Spherical vesicles known as liposomes, composed of lipid bilayers, can encapsulate hydrophilic drugs like doxorubicin (DOX) within their aqueous core. Polyethylene glycol (PEG) is frequently attached to the surface of liposomes through a process called

PEGylation, where PEG molecules are covalently bonded to the liposomal membrane. PEGylation enhances the nanoparticle's hydrophilicity, thereby extending its circulation duration by limiting opsonization and decreasing removal by the mononuclear phagocyte system (MPS).

Through the EPR effect, tumors take up PEGylated liposomes, as the abnormal vasculature permits nanoparticles to infiltrate and persist in the tumor microenvironment for longer durations. PEGylated liposomal DOX increases drug retention in TNBC tumors and reduces systemic toxicity, particularly cardiotoxicity, compared to free DOX [13,14].

3.2.1.2 PLGA nanoparticles for controlled drug release

Nanoparticle drug delivery systems commonly utilize poly(lactic-co-glycolic acid) (PLGA), a biodegradable polymer known for its versatility. PLGA nanoparticles are synthesized through methods such as emulsion-solvent evaporation, where the drug is initially incorporated into a polymer solution and then emulsified into water, allowing the formation of nanoparticles. Once the solvent evaporates, the nanoparticles are solidified, encapsulating the drug inside.

By modifying their size, surface charge, and hydrophobicity, these nanoparticles are optimized to increase their passive accumulation in tumor tissues through the EPR effect. Additionally, PLGA nanoparticles can be loaded with hydrophobic drugs such as paclitaxel. To improve the nanoparticles' stability and circulation time, they can also be PEGylated, similar to liposomes. The controlled degradation of PLGA allows for sustained drug release over time, providing continuous therapeutic effects and improving the drug's retention within TNBC tumors [13,16].

3.2.1.3. Solid lipid nanoparticles

Lipids that stay solid at room and body temperatures are used to formulate solid lipid nanoparticles (SLNs). High-pressure homogenization or solvent emulsification and evaporation methods are typically used to synthesize SLNs. In this process, the drug is either dissolved or dispersed in melted solid lipid, and nanoparticles are generated by cooling the lipid dispersion. Hydrophobic drugs like docetaxel can be encapsulated within SLNs, which passively accumulate in TNBC tumors via the EPR effect.

To enhance SLNs' stability and circulation time, surface modifications such as PEGylation or the addition of surfactants like poloxamers can be implemented. These modifications reduce the clearance of SLNs by the MPS, allowing them to circulate longer in the bloodstream. Once at the tumor site, the SLNs can release their payload, providing targeted drug delivery and minimizing systemic side effects [13,17].

3.2.1.4 Nanostructured lipid carriers

A combination of solid and liquid lipids is used to form nanostructured lipid carriers (NLCs), which are lipid-based nanoparticles. By incorporating liquid lipids, the drug-loading capacity is enhanced, and the likelihood of drug expulsion during storage is minimized. NLCs are typically prepared using high-pressure homogenization or microemulsion methods, where the lipid matrix is formed, and the drug is encapsulated within it.

To further enhance the accumulation of NLCs in TNBC tumors, they are often PEGylated or modified with other surface coatings like chitosan to improve circulation time and stability. Drugs like curcumin or doxorubicin are often loaded into NLCs, which are highly adaptable due to their capacity to deliver both hydrophilic and hydrophobic drugs. The sustained release profile of NLCs, combined with their improved tumor accumulation via the EPR effect, leads to prolonged therapeutic effects in TNBC [16,18].

3.2.1.5 Gold nanoparticles

Gold nanoparticles (AuNPs) are primarily used in PTT but can also serve as drug carriers. AuNPs are typically synthesized using methods such as Turkevich or citrate reduction, where gold salts are reduced to form nanoscale particles. By adjusting reaction conditions, the size and shape of AuNPs are able to be controlled, facilitating their optimized accumulation in tumors via the EPR effect.

PEG is frequently used to modify AuNPs, extending their circulation time and preventing aggregation within the bloodstream. Additionally, cancer cells can be actively targeted by attaching specific ligands, such as antibodies or small molecules, to the nanoparticle surface through functionalization. AuNPs have been employed to deliver chemotherapeutic agents like paclitaxel and doxorubicin, and in TNBC models, PEGylated AuNPs loaded with these drugs have shown enhanced tumor accumulation and reduced off-target effects [17,18].

3.2.2 Active accumulation

3.2.2.1 Antibody-conjugated nanoparticles

Antibody-conjugated nanoparticles represent one of the most extensively studied active targeting strategies. This technique employs monoclonal antibodies to modify the nanoparticle surface, allowing them to selectively attach to receptors that are highly expressed on TNBC cells. For example, nanoparticles can be functionalized with anti-EGFR antibodies to selectively bind to epidermal growth factor receptors, which are often highly expressed in TNBC cells.

The conjugation is achieved through chemical linkers such as carbodiimide (EDC) or N-hydroxysuccinimide (NHS), which covalently attach antibodies to the nanoparticle surface. This active targeting significantly enhances nanoparticle internalization by cancer cells, improving drug delivery efficiency. Studies have shown that antibody-conjugated PLGA nanoparticles loaded with paclitaxel can significantly increase cytotoxicity in TNBC cells compared to non-targeted formulations [13,14]

3.2.2.2 Folate-receptor targeted nanoparticles

The folate receptor is another well-known target for active accumulation in TNBC, as it is overexpressed in many cancers, including TNBC. Nanoparticles can be functionalized with folic acid (FA), a small molecule that binds to the folate receptor. Folic acid-modified nanoparticles are synthesized by attaching FA to the nanoparticle surface using linkers such as polyethylene glycol (PEG) or carbodiimide-based chemistry.

These nanoparticles exhibit enhanced cellular uptake in TNBC cells that overexpress the folate receptor, leading to higher drug concentrations within the tumor. In one study, folic acid-modified liposomes loaded with doxorubicin demonstrated significantly increased tumor uptake and reduced systemic toxicity in TNBC models [13,16].

3.2.2.3 Peptide-conjugated nanoparticles

Another strategy for active targeting is the use of tumor-homing peptides, which specifically bind to proteins overexpressed on cancer cells. For TNBC, peptides like RGD (arginine-glycine-aspartic acid), known to bind integrins found on tumor cells and the surrounding vasculature, have been commonly employed. Nanoparticles are functionalized with these peptides through covalent bonds, typically utilizing thiol groups from the peptide and maleimide or amine functionalities present on the nanoparticle surface.

RGD-modified AuNPs have been shown to selectively bind to TNBC cells and enhance the delivery of chemotherapeutics. These peptide-conjugated nanoparticles not only increase drug accumulation in tumors but also enhance the efficacy of therapies such as PTT by improving the heat generation at the tumor site [17].

3.2.2.4 Aptamer-conjugated nanoparticles

Short single-stranded DNA or RNA molecules, known as aptamers, can fold into distinct three-dimensional shapes, allowing them to bind with high affinity to specific target proteins. Aptamer-functionalized nanoparticles are synthesized by attaching aptamers to the nanoparticle surface, typically using thiol or amine coupling chemistry. These nanoparticles can target specific receptors highly expressed in TNBC cells, such as nucleolin or EGFR.

Nanoparticles conjugated with aptamers have demonstrated potential in improving the efficiency of drug delivery. For example, aptamer-functionalized liposomes loaded with chemotherapeutics have demonstrated higher cellular uptake and tumor accumulation in TNBC models, resulting in improved therapeutic efficacy and reduced drug resistance [18].

3.2.2.5 Transferrin-receptor targeted nanoparticles

The transferrin receptor (TfR) is commonly overexpressed in TNBC cells due to their high demand for iron. Transferrin (Tf)-conjugated nanoparticles are designed to exploit this overexpression by binding to TfR and facilitating receptor-mediated endocytosis. Tf can be attached to nanoparticles using chemical linkers such as EDC/NHS chemistry, and these nanoparticles can carry chemotherapeutics like doxorubicin or paclitaxel.

Tf-modified nanoparticles have demonstrated enhanced uptake by TNBC cells and improved intracellular drug delivery. This receptor-mediated targeting increases drug accumulation in tumor tissues while minimizing off-target effects [13,16].

3.3. Nano-based approaches developed for the treatment of TNBC

3.3.1 Photothermal therapy (PTT)

In PTT, light energy is transformed into heat by nanoparticles, enabling the selective destruction of cancer cells in a minimally invasive manner. AuNPs are frequently employed in TNBC treatment because of their strong near-infrared (NIR) light absorption and their capacity to effectively transform this light into heat.

AuNPs are typically modified with tumor-targeting ligands (e.g., RGD peptides or antibodies) to enhance their accumulation in TNBC cells. Once these AuNPs accumulate at the tumor site, NIR light is applied, leading to localized heating and subsequent cell death. PTT has shown promising results in TNBC, particularly when combined with other therapies such as chemotherapy. Studies have demonstrated that PTT using PEGylated AuNPs loaded with doxorubicin can significantly enhance the anti-tumor effect by inducing hyperthermia and increasing drug uptake [13,17].

3.3.2 Immunotherapy

Researchers are designing nanoparticles to improve the efficacy of immunotherapy in TNBC, focusing on the delivery of immunomodulators and therapeutic vaccines. To block cancer cells from evading the immune system, therapeutic agents like anti-PD-1/PD-L1 antibodies are delivered using lipid-based nanoparticles (LNPs) and polymeric nanoparticles, which are specifically engineered for this purpose.

Nanoparticles can also improve the transport of tumor-associated antigens to dendritic cells. improving antigen presentation and boosting the immune response against TNBC. For instance, mannose-modified LNPs target DCs and promote antigen presentation, leading to a more robust immune response. Moreover, nanoparticles can be loaded with immune stimulators like adjuvants to further activate immune cells, improving the overall therapeutic outcome [13,16].

3.3.3 Gene therapy

By introducing genetic material into cancer cells, gene therapy aims to silence oncogenes, restore the function of tumor suppressor genes, or alter the tumor microenvironment. To improve the delivery of gene-editing technologies like siRNA and CRISPR/Cas9 in TNBC treatment, researchers have employed nanoparticles.

For example, cationic lipid nanoparticles (CLNPs) are commonly used to encapsulate siRNA targeting genes like KRAS or PI3K, which are frequently mutated in TNBC. These nanoparticles are surface-modified with PEG or targeting ligands to improve delivery efficiency and protect the genetic material from degradation. Upon delivery, the nanoparticles release the siRNA into TNBC cells, leading to the downregulation of oncogenes and subsequent tumor regression [13,15].

3.3.4 Co-delivery

Co-delivery involves the use of nanoparticles to simultaneously deliver multiple therapeutic agents to TNBC cells. This strategy is particularly useful for overcoming drug resistance and targeting multiple pathways involved in TNBC progression.

Polymeric nanoparticles (PLGA) and lipid nanoparticles are frequently used for co-delivery, and they are designed to encapsulate both chemotherapeutic agents and molecular inhibitors. For instance, co-delivery of doxorubicin and PI3K/mTOR inhibitors using PLGA nanoparticles allows simultaneous targeting of TNBC cell proliferation and survival pathways. This combination significantly enhances the therapeutic efficacy while minimizing systemic toxicity [13,18].

Additionally, the co-delivery of chemotherapy and immunotherapy agents in a single nanoparticle system has also shown potential in enhancing the anti-tumor immune response, while reducing drug resistance. Liposomes co-loaded with gemcitabine and anti-PD-L1 antibodies have demonstrated promising results in preclinical models of TNBC [18].

4. Clinical progress of nano-based drug delivery systems in TNBC treatment

4.1. Nano-based products in TNBC treatment

Current research into nanoparticle-based therapies for TNBC is focused on enhancing drug delivery, minimizing systemic toxicity, and overcoming the challenges posed by TNBC’s aggressive nature and lack of specific molecular targets. Nanoparticles offer the potential to improve the therapeutic index of traditional chemotherapeutic agents by targeting tumor tissues more effectively through passive mechanisms such as the EPR effect, or active targeting using surface modifications like antibodies or ligands. Several nano-formulated drugs, such as Abraxane® and Doxil®, have already entered clinical practice, while others are in various stages of preclinical and clinical trials. These innovations aim to enhance drug bioavailability, reduce off-target effects, and improve patient outcomes. The table 1 summarizes key nanoparticle-based products that are currently being investigated or utilized in the treatment of TNBC.

Table1. Applications of nano-based drug delivery systems in the treatment of TNBC

Drug	Drug Delivery System	Mechanism	Clinical Result	Adverse Reaction	Ref.
Paclitaxel (Abraxane®)	Albumin-bound formulation	Improves solubility and tumor accumulation via EPR effect	Improved outcomes in metastatic TNBC with fewer side effects compared to conventional paclitaxel	Mild to moderate side effects, including neutropenia, neuropathy, hypersensitivity	[13]
Doxorubicin (Doxil®)	PEGylated liposomal formulation	Prolongs circulation, enhances tumor accumulation, reduces cardiotoxicity	Enhanced efficacy in TNBC with reduced cardiotoxicity, prolonged survival in clinical studies	Reduced cardiotoxicity compared to free DOX; adverse reactions include nausea, fatigue, stomatitis	[14]
Irinotecan (Onivyde®)	Liposomal formulation	Improves bioavailability and tumor accumulation	Increased tumor accumulation and bioavailability in TNBC models; studied for various cancers	Common adverse reaction include neutropenia, diarrhea, fatigue	[16]

Doxorubicin (ThermoDox®)	Heat-sensitive liposomal formulation	Releases drug in response to hyperthermia	Promising preclinical results in TNBC, enhanced drug targeting with localized heat	Potential for localized skin burns due to hyperthermia; similar side effects to doxorubicin	[17]
Gold Nanoparticles (AuNPs)	Gold nanoparticle-based delivery	Enhances PTT and drug delivery	Enhanced tumor inhibition in TNBC with potential for combination therapy (PTT)	Potential photothermal damage to surrounding tissues; further clinical validation needed	[18]
Polymeric Micelles (Genexol-PM®)	Polymeric micelles	Improves solubility, allows sustained release via EPR effect	Enhanced tumor accumulation, prolonged circulation, clinical trials show efficacy in TNBC	Mild side effects include nausea, fatigue, and neuropathy	[19]
Liposomal Cisplatin (Lipodox)	Liposomal formulation	Prolongs circulation time, enhances accumulation via EPR effect	Demonstrated improved outcomes in preclinical TNBC models, lower nephrotoxicity than free cisplatin	Potential renal toxicity, but less than free cisplatin; fatigue and nausea common	[20]
Paclitaxel (BIND-014)	Polymeric nanoparticles	Targets TNBC cells at prostate-specific membrane antigen	Demonstrated enhanced accumulation in TNBC, better efficacy compared to free paclitaxel in preclinical models	Potential for neutropenia and neuropathy; clinical trials ongoing for TNBC	[21]
CX-5461 (DNA-damaging nanoliposomes)	DNA-targeting nanoliposomes	Induces DNA damage specifically in cancer cells	Preclinical studies show promising tumor regression in TNBC models	Potential for hematologic toxicity and immune suppression; preclinical results only	[22]

4.2. Challenges in clinical trials of nano-based drug delivery system in TNBC treatment

The development of nano-based drug delivery systems for treating TNBC faces several significant challenges in clinical trials. TNBC is highly heterogeneous, both within and between tumors, making it difficult to design nanoparticle therapies that are universally effective. Different subtypes of TNBC may respond differently to the same treatment, complicating patient outcomes and limiting the broad applicability of these therapies. In addition, the TME of TNBC presents a major obstacle. The abnormal vasculature, hypoxic conditions, and immune-suppressive environment of TNBC tumors often hinder the efficient accumulation and penetration of nanoparticles, leading to suboptimal drug delivery despite the use of passive targeting mechanisms like the EPR effect.

Safety and toxicity concerns also pose challenges. Although nanoparticles are designed to reduce systemic toxicity, there remain concerns about their long-term safety, particularly their accumulation in non-target organs like the liver, spleen, and kidneys. Additionally, the clearance and degradation pathways of nanoparticles are not fully understood, raising the possibility of unforeseen side effects.

Furthermore, TNBC's propensity to develop drug resistance complicates the use of single-agent nanoparticle therapies, necessitating the creation of multi-functional nanoparticles capable of co-delivering multiple drugs. However, formulating stable and effective co-delivery systems remains technically challenging.

Manufacturing nanoparticles at a clinical scale presents another significant hurdle. The complex synthesis processes involved in nanoparticle production make it difficult to maintain consistency and reproducibility, which is crucial for regulatory approval. The lack of established regulatory frameworks specific to nanomedicine also contributes to delays in the clinical trial and approval processes. Finally, patient-specific responses to nanoparticle therapies are difficult to predict due to the lack of reliable biomarkers for patient stratification. These challenges highlight the complexities involved in developing effective nano-based drug delivery systems for TNBC, requiring ongoing advancements in nanoparticle design, clinical trial methodologies, and regulatory frameworks.

5. Conclusion

The use of nanotechnology-based drug delivery systems in the treatment of TNBC has demonstrated significant promise in overcoming various obstacles presented by this aggressive cancer subtype. By enhancing drug delivery to tumors through both passive and active targeting mechanisms, these systems improve therapeutic efficacy while minimizing systemic toxicity. Several nano-formulated drugs have already been successfully introduced into clinical practice, resulting in better patient outcomes. However, considerable challenges persist, including tumor heterogeneity, the complexities of the tumor microenvironment, safety issues, and regulatory obstacles. In light of these challenges, ongoing research and clinical trials are making steady progress, with the objective that nanomedicine will soon deliver more customized and efficient therapeutic solutions for patients with TNBC. Continued efforts are essential to refine nanoparticle designs, optimize delivery strategies, and improve patient stratification to fully maximize the clinical benefits of these innovative therapies.

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