

Drug delivery approaches for breast cancer

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Abstract: Breast cancer is one of the most common cancers affecting women worldwide. The controlled release of drugs to the precise site of the disease using a nanocarrier vehicle increases the therapeutic efficiency of the drugs. Nanotechnology-based approaches used to endorse clinical improvement from a disease also help to understand the interaction of malignant cells with their microenvironment. Receptor-based targeting is another approach for drug delivery which is undergoing clinical trials. Nanoparticles (NPs) delivery has been proven to promise high loading capacity, less toxicity, and stability of the drugs or biomolecules compared to traditional chemotherapeutic drugs. The goal of this review is to present the current problems of breast cancer therapy and discuss the NP-based targeting to overcome the hurdles of conventional drug therapy approach.

Keywords: breast cancer, nanoparticles, drug delivery systems

Introduction

Breast cancer is one of the most common cancers affecting women worldwide. In 2016, a total of 246,660 new cases of breast cancer and 14% of deaths due to breast cancer were reported in the US.¹ The majority of the deaths from breast cancer are due to its drug resistance and potential of metastasis to distant organs, such as the lymph nodes, bone, lung, and liver.^{2,3} It is well known that an ATP-binding cassette (ABC) family protein plays an important role in drug resistance in multiple malignancies, and its higher expression is proportional to higher resistance towards chemotherapy. Multidrug resistance (MDR) due to high expression of proteins such as P-glycoprotein (P-gp/ABCB1), ABCG2, and BCRP is a major hurdle in breast cancer prognosis and treatment. Although recent advances in immunotherapy have been made with the development of small molecules, proteins, and peptides, controlled-release drug delivery and targeting are still not achieved.

As indicated, the majority of the deaths from breast cancer are due to its potential of metastasis to distant organs.^{2,3} There are several pathways involved in the modulation of breast cancer and its progression to metastasis.⁴⁻⁶ There has been progress made in understanding the biological behavior of estrogen receptors (ERs), progesterone receptors (PRs), and human epidermal growth factor receptor 2 (HER-2) for multiple subtypes of breast cancer. Nanoparticles (NPs) carrying anticancer agents can be delivered actively or passively to targeted tumor to serve in diagnosis and treatment of breast cancer. NPs have multifunctional properties. In recent years, controlled release of therapeutic compounds from NPs has been achieved to determine the efficacy of the drug and to overcome MDR.

We previously reported the use of nanocapsules, nanospheres, and polymeric NPs for drug delivery, in which the drugs were physically and uniformly dispersed.⁷ NPs size and distribution are measured by photon correlation spectroscopy and verified

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by scanning or transmission electron microscopy (TEM) to determine the diameter of the particles.⁴ This technology of drug delivery using nanometer-sized particles could be the major therapeutic approach for future cancer patients. A recent progress in drug delivery technology is the design of surface-modified NPs that can improve the poor specificity and toxicological problems of antitumor therapy and act as a major therapeutic approach for patients. Primarily, the drug carriers used during the treatment act slowly for a longer period of time using specific stimuli. The conventional chemotherapeutic drugs affect both normal and cancer cells, whereas NP-coated drugs accumulate in tumors through enhanced permeability.⁸

The application of NPs in medicine has enabled the development of nano-formulated drug delivery approach. There are several types of drug carriers commonly available such as polymeric dendrimers, micelles, microspheres, liposomes, quantum dots (QDs), nanoemulsions, gold nanoparticles (GNPs), and hydrogels, which require various methods of drug attachment including encapsulation, covalent binding, and adsorption.^{9,10} For example, lipid-based NPs can activate the secretion of glucagon-like peptide 1 for the treatment of

human diabetes mellitus type-2.¹¹ Several other applications of nanomaterials such as carbon nanotubes, silver, and silica nanocarriers have been promoted in the biomedical field, and these nanomaterials are used during the treatment of various neurological and cancer diseases.¹²⁻¹⁴ Recently, next-generation nano-formulated platinum-based drug delivery has been used in clinics for cancer.¹⁵

The receptor (HER-2, epidermal growth factor receptor [EGFR], vascular endothelial growth factor receptor [VEGFR], insulin-like growth factor I receptor [IGF-IR])-based targeting is the approach which is correlated with the breast tumorigenesis and is undergoing clinical trials (Phases II and III).¹⁶ Among them, the most common type of breast cancer, which affects one in five women, is HER-2-positive breast cancer caused due to the overexpression of HER-2 on the surface of the breast tumor and characterized by poor prognosis and aggressive growth. An overview of the ongoing breast cancer clinical trials based on targeted therapy and chemotherapy drugs is presented in Table 1. Moreover, antibody-NP conjugates also facilitate the loading of higher drug concentrations for targeted delivery. For example, liposomes formulated with the monoclonal antibodies

Table 1 Overview of ongoing breast cancer clinical trials based on targeted and chemotherapeutic drugs

Therapeutic agents	Target cancer subtypes	Clinical trial phases	Type	Status	Trail ID reference (ClinicalTrials.gov)
Trastuzumab	HER-2-positive and locally advanced/metastatic breast cancer	Phase III, Phase II	Biomarker/laboratory analysis, treatment	Active	MM-302-02-02-03
Neratinib plus capecitabine vs lapatinib plus capecitabine	HER-2-positive metastatic breast cancer	Phase III	Treatment	Active	PUMA-NER-1301
Talazoparib (BMN 673), a PARP inhibitor	Advanced and/or metastatic breast cancer patients with BRCA mutation	Phase III	Treatment	Active	673-301
Fulvestrant and/or anastrozole	Postmenopausal patients with stage II-III breast cancer undergoing surgery	Phase III	Treatment	Active	A011106
Olaparib	Triple-negative nonmetastatic breast cancer	Phase III	Biomarker/laboratory analysis, natural history/epidemiology, treatment	Active	NSABP-B-55
Carboplatin and paclitaxel with or without veliparib (ABT-888)	ER2-negative metastatic or locally advanced breast cancer	Phase III	Treatment	Active	M12-914
Palbociclib (PD-0332991) + letrozole vs placebo + letrozole	ER-positive/HER-2-negative advanced breast cancer	Phase III	Biomarker/laboratory analysis, treatment	Active	A5481027
Platinum-based or capecitabine chemotherapy	Triple-negative basal-like breast cancer	Phase III	Biomarker/laboratory analysis, treatment	Active	EAI131
Doxorubicin hydrochloride and cyclophosphamide followed by paclitaxel with or without carboplatin	Triple-negative breast cancer	Phase III	Biomarker/laboratory analysis, treatment	Active	NRG-BR003
Margetuximab plus chemotherapy vs trastuzumab plus chemotherapy	HER-2-positive metastatic breast cancer	Phase III	Treatment	Active	CP-MGAH22-04

(Continued)

Table 1 (Continued)

Therapeutic agents	Target cancer subtypes	Clinical trial phases	Type	Status	Trail ID reference (ClinicalTrials.gov)
Pembrolizumab (MK-3475) vs single-agent chemotherapy	Metastatic triple-negative breast cancer	Phase III	Treatment	Active	3475-119
Pembrolizumab (MK-3475) plus chemotherapy vs placebo plus chemotherapy	Metastatic triple-negative breast cancer	Phase III	Biomarker/laboratory analysis, treatment	Active	3475-355
Trastuzumab in treating leptomeningeal metastases	HER-2-positive breast cancer	Phase II, Phase I	Biomarker/laboratory analysis, treatment	Active	NU 10C03
BB1608 administered with paclitaxel	Advanced malignancies	Phase II, Phase I	Treatment	Active	BB1608-201
Imiquimod, cyclophosphamide, and radiation therapy	Breast cancer with skin metastases	Phase II, Phase I	Treatment	Active	NYU 11-00598
Dovitinib lactate in combination with anastrozole, exemestane, or letrozole	Hormone-receptor-positive metastatic breast cancer	Phase II, Phase I	Biomarker/laboratory analysis, treatment	Active	2010-535
Tyrosine kinase inhibitor PLX3397 and eribulin mesylate	Triple-negative breast cancer	Phase II, Phase I	Biomarker/laboratory analysis, treatment	Active	12751
Triciribine phosphate, paclitaxel, doxorubicin hydrochloride, and cyclophosphamide	Stage IIB–IV breast cancer	Phase II, Phase I	Treatment	Active	2011-269
GDC-0810 single agent or in combination with palbociclib and/or a luteinizing hormone-releasing hormone agonist	Locally advanced or metastatic ER-positive breast cancer	Phase II, Phase I	Biomarker/laboratory analysis, treatment	Active	GO29642
LEE011, BYL719, and letrozole	Advanced ER-positive breast cancer	Phase II, Phase I	Biomarker/laboratory analysis, treatment	Active	CLEE011X2107
Nivolumab combined with ipilimumab	Advanced or metastatic solid tumors	Phase II, Phase I	Treatment	Active	CA209-032
MLN0128 in combination with exemestane or fulvestrant	ER/PR-positive metastatic breast cancer	Phase II, Phase I	Biomarker/laboratory analysis, treatment	Active	C31001
Romidepsin and paclitaxel albumin-stabilized nanoparticle formulation	Metastatic inflammatory breast cancer	Phase II, Phase I	Treatment	Temporarily closed	13C.387
Ruxolitinib phosphate and trastuzumab	Metastatic HER-2-positive breast cancer	Phase II, Phase I	Treatment	Active	AAAM1906
Gemcitabine hydrochloride, trastuzumab, and pertuzumab	HER-2-positive metastatic breast cancer	Phase II, Phase I	Treatment	Active	MCC-17656
PI3K inhibitor BYL719 and paclitaxel albumin-stabilized nanoparticle formulation	HER-2-negative stage III or IV breast cancer	Phase II, Phase I	Biomarker/laboratory analysis, treatment	Active	CBYL719XUS06T

Abbreviations: HER-2, human epidermal growth factor receptor 2; PARP, poly (ADP-ribose) polymerase; ER2, estrogen receptor 2; ER, estrogen receptor; PR, progesterone receptor.

act against tumor cell antigens.¹⁷ Nanocarrier-based and clinically approved therapeutic drug conjugates used to target metastatic breast cancer are shown in Tables 2 and 3. Targeted drug nanocarriers could replace the current method of treatment of chemoresistant tumor cells and cure cancer. In this review, we discuss the various drug delivery platforms (systemic, localized, and receptor-based) used for the model of breast cancer therapy (Figure 1).

Systemic drug delivery approaches

Nanocarrier-based drug delivery systems for chemotherapeutic drugs act efficiently on multiple malignant sites. The most

common drug delivery approaches are based on organic and inorganic particles. The organic particles used for drug delivery application are micelles, liposomes, polymers, dendrimers, and nanogels. They have versatile surface building blocks for efficient endocytosis and loading. NPs have a multifunctional surface-modifying property that directs the cell to the tumor vasculature. The technology of encapsulating chemotherapeutic drugs using a nano-scale device is the best approach with regard to decreased side effects and improved bioavailability of drugs for breast cancer. While emerging technologies of systemic drug delivery using NPs promise early treatment of breast cancer, at present, limited options

Table 2 Nanocarrier-based therapeutic drug conjugates to target metastatic breast cancer

Nanoparticle carrier composition	Therapeutics	Action	References
Polyethylene glycol-poly(d,l-lactide-co-glycolide)	Paclitaxel + Isonidamide	EGFR	18
Poly(N-methyl-dietheneamine-sebacate)-co-[(cholesteryloxycarbonylamido ethyl) methyl bis (ethylene ammonium bromide) sebacate Bio-nanocapsule/liposome	Paclitaxel + siRNA	Downregulation of Bcl-2 and increased cytotoxicity in MDA-MB-231 cells	19
	Z _{HER-2} -BNC + siRNA	Gene silencing and protein knock down in HER-2-expressing breast cancer cells	20
Polyethylene glycol-block-poly(N-hexyl stearate l-aspartamide)	Doxorubicin + wortmannin	Passive, metastatic breast cancer	21
Polyethylene glycol-liposome	Quercetin+vincristine	Passive, metastatic breast cancer	22
Cationic, anionic polyethylene glycol-liposome	siRNA + doxorubicin	Passive, metastatic breast cancer	23
N-(2-hydroxypropyl) methacrylamide copolymer	Trastuzumab + PKI 166	Active, HER-2 breast cancer	24

Abbreviations: EGFR, epidermal growth factor receptor; BNC, bio-nanocapsule; HER-2, human epidermal growth factor receptor 2.

are available to the patients with metastatic breast cancer. Based on nanocarrier platforms, the most relevant strategy for precise site targeting in drug-resistant breast tumor cells is shown in Figure 2.

Organic drug delivery approaches

Micelles

Polymeric micelles (PMs) are colloidal particles prepared from conjugates of water-soluble polymers with phospholipids or long-chain fatty acids and other surfactants. Micelles are used for the delivery of water-insoluble chemotherapeutic drugs. They were first proposed by Paul Ehrlich for targeted drug delivery to diseased cells. Micelles accumulate at poorly vascularized tumors and enhance permeability and

retention, and increase the half-life of anticancer agents.⁴⁴ They have been shown to overcome P-gp efflux, act through receptor-mediated endocytosis, and increase intracellular drug concentration with enhanced cytotoxicity in MCF-7/ doxorubicin-resistant cells.^{45,46} Moreover, fabricated immune micelles (antibodies bound to the surface of micelles) were also used in breast adenocarcinomas. Treatment of HER-2-positive breast cancer was performed with anti-HER-2 monoclonal antibody (mAb), fabricated with antibody-conjugated lysosomal P (LA-co-TMCC)-g-PEG-furan micelles.⁴⁷ Use of anti-HER-2 antibody complex micellar formulation in HER-2-positive and HER-2-negative cells has shown high efficacy of taxol compared to simple lipid-based protein.⁴⁸ In another study of the use of paclitaxel

Table 3 Additional clinically approved chemotherapeutic drug combination for metastatic breast cancer prevention

Agents	Drug combinations	Action	References
Monoclonal antibodies	Trastuzumab + doxorubicin + cyclophosphamide;	Improved overall survival and response rate, while cardiomyopathy and hematological toxicity were observed	16, 25
	trastuzumab + epirubicin + cyclophosphamide		
	Trastuzumab + paclitaxel; trastuzumab + gemcitabine; trastuzumab + vinorelbine	Progression-free survival with hematological toxicity	26
	Cituximab + cisplatin	Improved response rate in TNBC with neutropenia and dyspnea	27
Tyrosine kinase inhibitor based	Lapatinib + (capecitabine, paclitaxel, letrozole); sunitinib + docetaxel; erlotinib + cisplatin + gemcitabine	Improved response rate and overall survival, but toxicity, diarrhea, and skin rashes were the side effects	28–32
Anthracycline based	Anthracycline-based doxorubicin + cyclophosphamide; doxorubicin + fluorouracil; epirubicin + fluorouracil/cyclophosphamide	Improved response rate while related toxicity and no significant difference in progression or survival were observed	33
Taxane based	Doxorubicin + paclitaxel; doxorubicin + docetaxel; capecitabine + docetaxel; gemcitabine + paclitaxel	Improved response rate, progression-free survival, and relapse-free survival, but side effects such as cardiotoxicity, hematological toxicity, and increased diarrhea were found	34–38
Other chemotherapeutic regimen combinations	Ixabepilone + capecitabine	Improved response rate but peripheral neuropathy was observed	39
	Cyclophosphamide + methotrexate + fluorouracil	Overall improved survival and relapse-free survival, but loss of bone was a disadvantage	40–42
	Trastuzumab + lapatinib	Improved patient survival, and overcome toxicity issue with trastuzumab	43

Abbreviation: TNBC, triple-negative breast cancer.

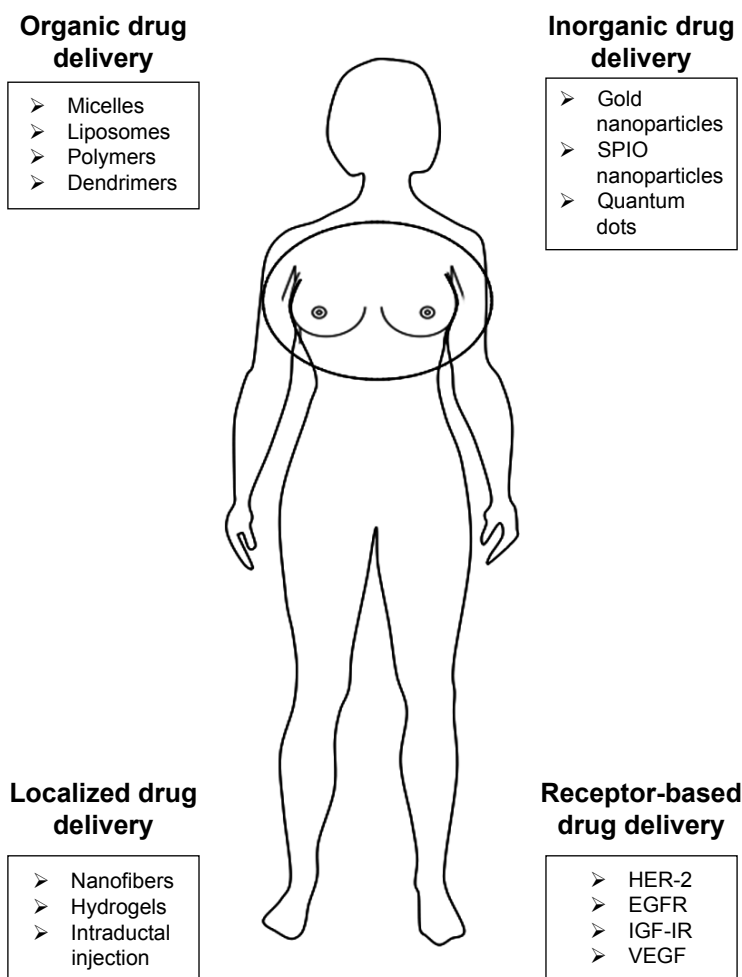


Figure 1 Drug delivery systems for breast cancer.

Abbreviations: SPIO, superparamagnetic iron oxide; HER-2, human epidermal growth factor receptor 2; EGFR, epidermal growth factor receptor; IGF-IR, insulin-like growth factor I receptor; VEGFR, vascular endothelial growth factor receptor.

PM formulation in metastatic breast cancer patients, the Genexol-PM response rate was observed to be 58.5% compared to plain drugs that are in clinical trial Phases I and II. However, in SK-BR-3 cells, antibody-decorated NPs have shown 53.4% and 38.6% higher cellular uptake than the plain micelles in Phases I and II, respectively.⁴⁹

Liposomes

Liposomes are spherical vesicle microparticles that contain single or multiple bilayered membrane structures and were first described in 1965.^{8,50} Their size varies from 50–200 nm and they have a tendency to accumulate in tumor cells with an enhanced permeability and retention. Liposomes are classified based on size and composition and influenced by several factors such as bilayered fluidity, surface charge, surface hydration, and methods of preparation.⁵¹ Liposomes have been reported to encapsulate lipophilic and hydrophobic drugs which are stable, nontoxic, biocompatible,

biodegradable, and non-immunogenic.⁵² Moreover, liposomes are reported to play a role in direct inhibition of P-gp by anionic membrane lipids. A previous study on Rhodamine retention using P-gp and BCRP substrate in breast cancer cell line MCF-7 showed that liposome encapsulation was increased in MCF-7/P-gp cells compared to MCF-7/wild-type cells.⁵³ Liposomes are reported as an effective delivery system for siRNA- or oligonucleotide-based therapy, and liposome-based drug formulations are currently used in clinical protocols.⁵⁴ The encapsulation of drugs in liposomes reduces the toxicity through biodistribution. The therapeutic application of liposomes as a drug carrier for the delivery of paclitaxel has also been evaluated in human ovarian cancer.^{55,56} Due to their small size and prolonged circulation, liposomes (including PEGylated liposomes) can provide protection from mononuclear phagocytes. PEGylated liposomes formulation with NPs coated on the surface using polyethylene glycol (PEG) improved the efficacy of drug

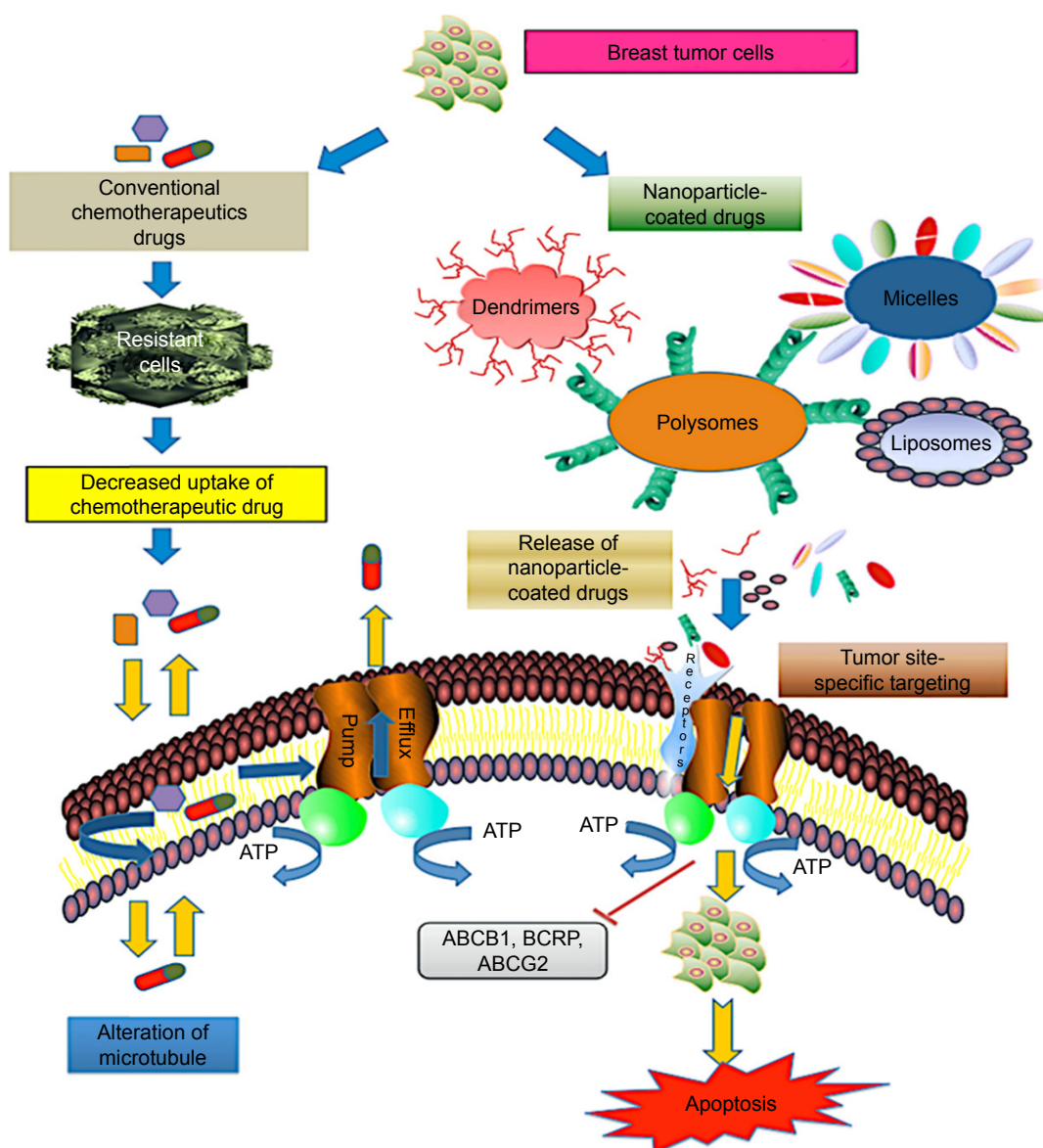


Figure 2 Schematic representation of nanoparticle-based drug delivery mechanism in drug-resistant breast cancer cells. The most common mechanism of drug efflux in cancer cells is mediated by ABC transporters P-glycoprotein, BCRP, and ABCG2. Multidrug resistance protein consisting of nuclear-binding domain and transmembrane domain binds to the receptors on the surface of target tumor cells and functions in efflux of chemotherapeutic drugs such as taxol and anthracycline. However, delivery approaches using targeted drug nanocarriers (dendrimers, liposomes, micelles, polysomes) overcome the chemoresistance in tumor cells by activation of proapoptotic mediators, resulting in cell death.

Abbreviation: ABC, ATP-binding cassette.

delivery to target cells.⁵⁷ Yang et al reported that PEGylated formulation of paclitaxel increased the half-life compared to conventional liposomes formulation.⁵⁸ The combinations of doxorubicin and cyclophosphamide utilizing non-PEGylated liposomes were used for the treatment of metastatic breast cancer.⁵⁹ Moreover, liposome-conjugated antibody that overexpresses the HER-2 has been developed and reported as delivering 22-fold more calcein to mammary epithelial cells.⁶⁰ The synergistic effects of combined drug delivery of quercetin and vincristine through liposomes were reported for treatment of ER-negative breast cancer.⁶¹

Polymers

Polymeric NPs (size 3–200 nm) that are formulated by binding a copolymer to a polymer matrix are widely used as drug delivery carriers. Polymers are classified as natural, synthetic, biodegradable, and nonbiodegradable forms. The most commonly used natural polymers are cellulose, chitosan, alginate, and gelatin, which are mildly immunogenic in nature. In addition, modified polymers with precise chemical composition increase the efficacy of site-specific targeting. Moreover, synthetic polymers such as poly- ϵ -caprolactone (PCL), poly-(lactic-co-glycolide), and polylactide (PLA)

have a high rate of solubility and permeability. Such polymers are biocompatible and biodegradable with slow degradation rate, with good drug stability and release. Numerous polymer–drug conjugates, such as poly(d,l-lactide-co-glycolide) (PLGA), PEG, dextran, and N-(2-hydroxypropyl) methacrylamide (HPMA), have been tested in drug delivery research.²⁴ Chemotherapeutic drugs like paclitaxel, doxorubicin, camptothecins, and platinates have been clinically tested in drug conjugates for multiple cancers. It has been shown that polymeric NPs have a higher loading capacity for poorly water-soluble drugs, more stability, and more physicochemical properties (solubility, stability) compared to liposomes. The hybrid PM, developed by coating a PEG–phospholipid copolymer envelope on a nuclear PLGA NP, has improved therapeutic index with reduced toxicity.⁶² A cisplatin-modified Pt(IV)-based PLGA-PEG NP was also reported with a significantly improved efficacy in breast cancer patients.⁶³ Lee and Nan proposed a novel combination of the drug delivery system for HER-2-overexpressing metastatic breast cancer via HER-2-targeted HPMA copolymer conjugates in combination with a tyrosine kinase inhibitor (PKI-166). Their study on targeting HER-2 receptors via extracellular (via TRZ binding) and intracellular (via PKI-166 binding) kinase domains suggested the synergistic effect from a drug conjugate delivery system for anticancer activity.²⁴ Therefore, a novel drug delivery system using a polymer with different mechanisms of action can bring forth a promising targeted therapy to overcome the limitations of the individual drug.

Dendrimers

Dendrimers are highly branched macromolecules possessing low polydispersity index. In 1978, Vogtle first described the nanotechnology platforms for drug delivery using dendrimers.⁶⁴ Like other nanocarriers, the biocompatibility and pharmacokinetics of dendrimers are easy to predict and can be controlled. There are various drug platforms that have been synthesized as delivery vehicles such as polyetherhydroxylamine (PEHAM), polyamidoamine (PAMAM), polyesteramine, polypropyleneimine, and polyglycerol.⁶⁵ The biopermeability of cationic PAMAM-NH₂ (G0–G4) dendrimers across the biological membranes was evaluated for oral drug delivery which revealed that they crossed the membrane by paracellular and endocytosis pathways.^{66,67} The water solubility and size of dendrimers increased by PEGylation which helped to improve the retention and biodistribution characteristics. Several groups have shown that cell toxicity strongly correlates with the dendrimers end. The surface functional groups of dendrimers are amines

that are decorated with protons, benzyloxycarbonyl- or tert-butoxycarbonyl-protecting group's ethylenediamine ligands, or dansyl fluorescence labels. The doxorubicin-containing polyion complex micelle accumulates in the nucleus of drug-resistant MCF-7 cells and is also considered to have a potent antiproliferative effect on targeted tumor.⁶⁸ The cytotoxicity of MCF-7 breast cancer cells was examined *in vitro* using low-generation (G0, G1, and G2) PAMAM-like polymers.⁶⁹ However, dendrimers–drug conjugate has an antineoplastic agent and is covalently attached to the peripheral groups of the dendrimers, and has distinct advantages over drug-encapsulated systems. For local delivery in breast cancer, doxorubicin-G4-PAMAM complexes were encapsulated into the liposomes. These were formulated with HEPC and showed enhanced activity towards the MDA-MB435 breast cells compared to the individual dendrimers.⁶⁵ Thus, the methods for delivering the dendrimers-based NPs for transport of drugs into the specific area of malignant cells could be the best approach for delivery of NPs and to treat cancer cells.

Inorganic drug delivery approaches

Gold nanoparticles

GNPs are used in chemotherapy for several cancers. Due to their small size (approximately 130 nm) and specificity, they circulate throughout the tumor cells. GNP coating acts as a biomarker for the cancer diagnosis and is used as a probe for transmission electron microscopy and antimicrobial agents. There are several methods available for GNP production; the most common is the one involving citrate reduction of gold in water and the Brust–Schiffrin method.⁷⁰ The conjugation of GNPs to transferrin molecules was tested in breast cancer cells, and the results showed higher cellular uptake of transferrin molecules bound to GNPs in comparison to unbound molecules.⁷¹ PEG-conjugated liposomes were used for anticancer drug delivery.⁷² Balakrishnan et al targeted the breast cancer EGFR/VEGFR-2 signaling pathway using AuNPs-Qu-5, and reported its role in inhibition of migration, invasion, angiogenesis, and metastasis of breast cancer cells. This group has studied significant inhibition of multiple proteins such as p-PI3K, Akt, Snail, Slug, vimentin, N-cadherin, and p-GSK3 β with treatment with AuNPs-Qu-5.⁷³ Eissa et al investigated 120 patient samples for ER, PR, and HER-2 status and reported that histidine-rich glycoprotein RNA-AuNPs had 90% sensitivity and specificity and can act as a diagnostic marker for breast cancer prognosis.⁷⁴ Another report showed that triple-negative breast cancer MDA-MB-231 cells were inhibited by phytochemical compounds such as gallic acid capped with GNPs.⁷⁵

SPIO-NPs

Superparamagnetic iron oxides (SPIOs) are used in tissue repair, immunoassay, and for cellular imaging in a magnetic field. They are also used as magnetic resonance contrast agents, controlling the direction of magnetic force to allow monitoring of the physiological and molecular changes in the body. SPIO nanoparticles (SPIO-NPs) have the ability to control the physical and chemical properties of particles such as their shape, size, and surface chemistry. SPIO-NPs have several applications in detection of inflammatory diseases and targeting of surface markers on tumors. SPIO consists of two components, an iron oxide core and a hydrophilic coating of the magnetic particle biomolecule, which allow it to deliver nano-derived biomolecules in a targeted area.⁷⁶ Biopolymers such as PEG, polyacrylic acid, dextran, alginate, polyethylene imine, and poly (vinyl alcohol) (PVA) are used as coating reagents for the surface stabilization of SPIOs.⁷⁷ They bind to tumor sites for delivery of antibodies, enzymes, proteins, drugs, or nucleotides. The uptake of SPIO-loaded PLA-tocopheryl PEG succinate (SPIO-PNPs) by MCF-7 breast cancer cells was confirmed through TEM in several experiments.⁷⁸ SPIO-targeted biomarkers have been developed for tumor cell imaging and detection. SPIO-Herceptin detects overexpression of HER-2/neu (c-erbB-2) tyrosine kinase receptor in the metastatic breast cancer.⁷⁹ SPIOs most efficiently used in magnetic resonance imaging and macrophage processing. However, knowledge concerning breast cancer and metastatic lymph nodes injection of SPIOs is lacking and needs to be explored. In future, SPIO-NPs could be applied as an effective treatment agent in breast cancer therapy.

Quantum dots (QD)

QD nanocrystals have a tunable wavelength, high brightness, anti-photo bleach, and optical properties, and are used as probes for many biological and biomedical applications. The conjugation of surface-modified QDs with antibodies, peptides, or other biomolecules enables their application in clinical oncology targeting. Bae et al synthesized a bimodal imaging nanoprobe by conjugating monoclonal antibodies and perfluorocarbon (PFC)/QD nanoemulsions for the detection of surface antigens on breast cancer cells (SK-BR-3, MCF-7, MDA-MB468) and also proposed that PFC/QD nanoemulsion had a great capacity for imaging therapy of tumor cells.⁸⁰ Several studies have shown the potential of QDs usage for various applications, including imaging, cell tracking, immunolabeling, in situ hybridization, and other in vitro- and in vivo-related technologies.

Localized drug delivery approaches

The current treatment for recurrent breast cancer is based on chemotherapeutic drugs, radiation, or surgery depending on location and the stages of the tumor. Localized drug delivery has more impact as a therapeutic option for early-stage cancers compared to the systemic drug. There are natural (dextran, chitosan, hyaluronic acid, gelatin, collagen polypeptides) and synthetic polymers that are used intratumorally in the cancerous tissue for drug delivery to cure breast cancer.⁸¹ Furthermore, hydrogel formation of the NPs or polymers system, nanofiber with versatile morphology and tensile strength, and intraductal injection using microcatheter enhance the performance of ongoing smart drug delivery therapy.

Nanofibers

A nanofiber is a cross-linked polymer characterized by tensile strength and chemical nature. Biodegradable polymers such as PEG, PLGA, chitosan, PVA, PLA, polyethylene oxide, and PCL are used for preparing nanofibers for drug delivery applications. Another type of nanofiber, electrospun, was found to be bioactive and biocompatible similar to a human extracellular matrix, which supports diverse cells to grow into fabricated tissues.⁸² A nanofiber-based platform has been prepared to evaluate migration of metastatic breast cancer cells. Curcumin-loaded PCL nanofibers were tested in breast cancer cell line MCF-7, and exhibited 15% more cytotoxicity compared to the commercial drug.¹⁶ The use of a nanofiber model could allow testing the efficacy of an anticancer drug in diagnostic tools for multiple malignancies.

Hydrogels

Hydrogels are water-insoluble molecules, chemically or physically linked into a polymer chain. They allow controlled release of a drug within the body. Drugs enclosed within a hydrogel correspond to swell, diffusion, and control of the chemicals. Hydrogels for tumor cell therapy are developed in the form of microspheres or NPs. They are fabricated using protein and glycosaminoglycan components of breast tissue, which stimulate the growth of human breast cells. The most common endothermal hydrogel was based on chitosan, which is formed in tumor tissue after intratumor injection.⁸³ Chitosan hydrogels based on temperature-responsive hydroxyl butyl, poly (vinyl alcohol), thermo sensitive poly (ethylene glycol)-grafted, chitosan chloride/glycerophosphate and chitosan/bifunctional aldehyde have been investigated, but not tested in the preclinical trial for breast cancer

application. However, only a few of the hydrogels have in situ gelling properties. Another platform for local and sustained delivery with high efficiencies in *in vitro* and *in vivo* breast cancer mice model was reported via siRNA encapsulation in oligopeptide-terminated poly(β -amino ester) NPs. Moreover, sustained delivery was enhanced when NPs were embedded in a hydrogel scaffold.⁸⁴

Intraductal injection

The molecular and morphological changes that occur in breast ductal epithelium cells are associated with a high risk of breast cancer. Ductal carcinoma *in situ* is a noninvasive early cancer, occurring in the lining of the breast milk duct, and represents 80% of breast cancers diagnosed. The use of microcatheter for collecting ductal cells can improve the ductal epithelium cells detection in abnormal breast cells. Ductal lavage procedure using microcatheter has been reported for cytological analysis with high efficiency for collecting breast epithelial cells. A study of 507 women who had a high risk of breast cancer was conducted to evaluate nipple aspirate fluid and ductal lavage and proved that ductal lavage was more sensitive and safer than nipple aspiration.⁸⁵ Moreover, chemotherapy through localized drug delivery was achieved by intraductal injection of chemotherapeutic drugs 5-fluorouracil and estradiol into mammary papilloma for the improvement of the immune response.⁸⁶ Detection of ductal cellular abnormalities can provide additional information to reduce the risk of breast cancer and also help in ongoing drug therapy.

Receptor-based drug delivery approaches

Breast cancer growths are regulated by multiple receptors, and inhibition at the receptor provides a new avenue for cancer therapy. Studies on receptor targeting are being used in clinical trials in patients with metastatic breast cancer. Although multiple cytotoxic drugs, such as gemcitabine, nab-paclitaxel, doxorubicin, etoposide, and vinorelbine, have been developed, the overall survival rates are still less.⁸⁷ Several studies have focused on receptors HER-2, EGFR, IGF-IR, and VEGFR, which revealed specific targets for breast cancer cells. According to those studies, HER-2 belongs to EGFR family and is poorly differentiated in triple-negative breast cancer; IGF-IR is regulated by tyrosine kinases, whereas VEGFR works as a stimulus for angiogenesis. The receptor-based targeting approach is illustrated in Figure 3.

HER-2

HER-2 has been reported to be overexpressed in breast cells. It belongs to the EGFR family and strongly correlates with tumorigenesis. Anti-HER-2 therapy using nanocarrier drugs and antibody-directed therapy for the antigen-binding site could be an effective treatment for breast cancer. Trastuzumab (mAb) has shown an overall response rate of 15%–30% against the extracellular domain of HER-2-positive breast cancer cells when given individually, but in combination with taxanes or vinorelbine, the response rates were 50%–80%.⁸⁸ In a randomized clinical trial Phases II and III, the overall percentage survival and the response rate were demonstrated to be high when combination therapies of trastuzumab with chemotherapeutic drugs were given to breast cancer patients.¹⁶ Blockade of receptor using inhibitors may improve the treatment of trastuzumab-resistant tumors. A tyrosine kinase inhibitor, such as lapatinib, blocks the expression of EGFR (ErbB1) and HER-2 (ErbB2), which are co-expressed in 30% of breast cancers. The Phase II trial has shown 33% response rate after treatment of HER-2-positive metastatic breast cancer with lapatinib.⁸⁹ Another inhibitor gefitinib (an EGFR tyrosine kinase inhibitor) and pertuzumab (mAb) were reported to be able to block the overexpression and hetero-dimerization of HER-2 receptor family.⁹⁰ Moreover, adjuvant therapy of chemotherapeutic drugs can enhance the overall survival rate of breast cancer patients.

EGFR

Overexpression of EGFR has been reported in poorly differentiated triple-negative and inflammatory breast cancer cells. EGFR gene was identified in the early 1980s, and the clinical interest in the gene began in the late 1990s with the development of inhibitors.⁹¹ There are several members of EGFR family reported, including EGFR (also known as ErbB1 and HER-1), HER-2 (also known as HER-2/neu and ErbB2), ErbB3 (HER3), and ErbB4 (HER4). Out of these, HER-2 was overexpressed in breast cancer.^{92,93} It has been proven that the EGFR expression was correlated with an increased copy number of the gene and protein overexpression in breast cancer. The increased EGFR gene copy number and protein overexpression were observed in ER-negative, PR-negative, HER-2 negative (triple-negative) breast cancer patients. Although drugs including cetuximab, lapatinib, gefitinib, and others have been developed to target the EGFR, the overall clinical outcome is poor. EGFR signaling and the relationship between triple-negative and inflammatory breast cancer-targeted therapies are the current topic of interest in the field of breast tumor therapy. Several clinical trials

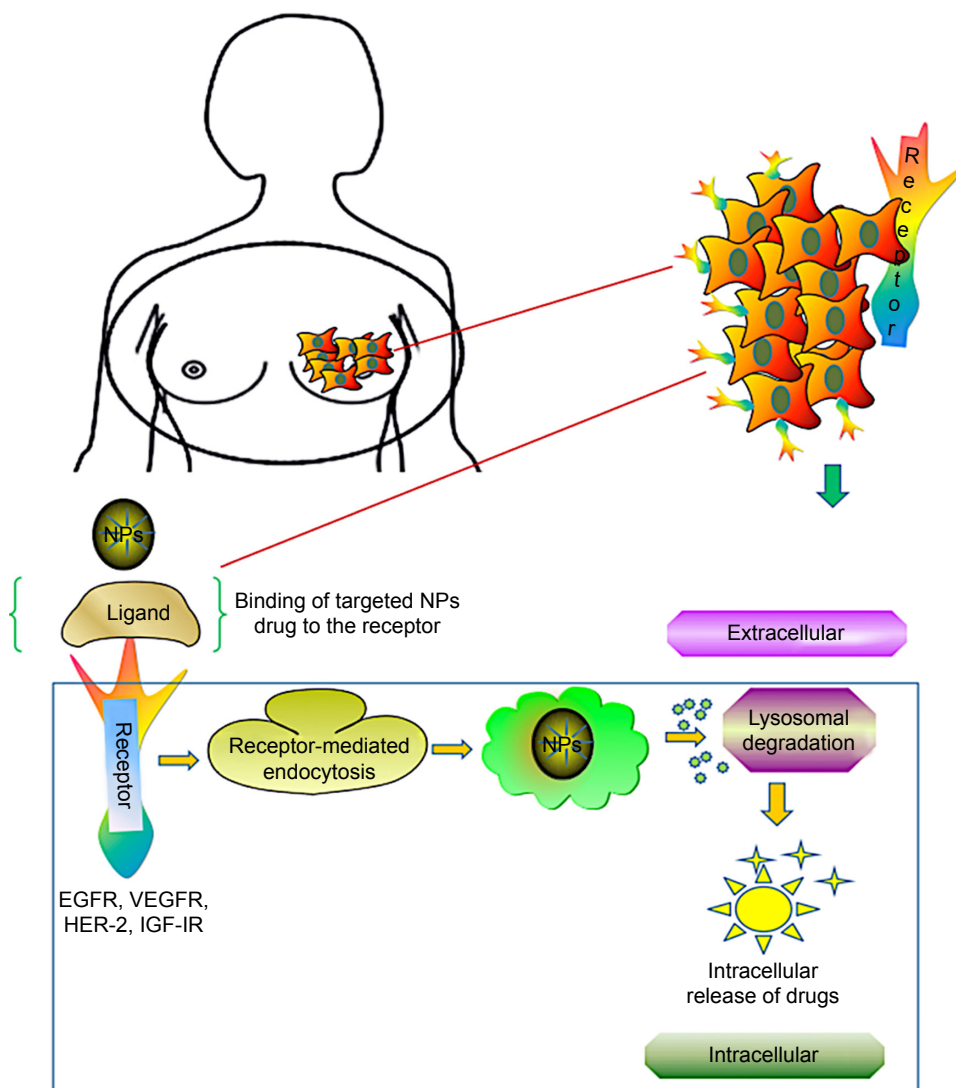


Figure 3 Receptor-mediated drug delivery to metastatic breast cancer cells. Nanocarrier-based drug targeting using receptor-mediated pathways governs the major therapeutic approach for the active sites in tumor cells. Ligand–nanoparticle conjugate binds to the receptors (EGFR, VEGFR, HER-2, IGF-IR) on the membrane, mediates internalization of nanoparticles through endocytosis, and releases the drugs by lysosomal degradation to the active sites of tumor cells.

Abbreviations: EGFR, epidermal growth factor receptor; VEGFR, vascular endothelial growth factor receptor; HER-2, human epidermal growth factor receptor 2; IGF-IR, insulin-like growth factor I receptor; NPs, nanoparticles.

investigating vascular endothelial growth factor (VEGF), EGFR, Src, and mTOR molecular markers, for the treatments of triple-negative breast cancer, are ongoing; other inhibitors of the PI3K/AKT/mTOR pathway for deregulation in triple-negative breast cancer are in early-phase clinical trials.

IGF-IR

Breast cancer growth is regulated by receptor tyrosine kinases (RTKs), and the inhibition of the receptors, thus, could be the targets for anticancer therapy. The growth and differentiation of normal breast cells are mediated by IGF-IR signaling. Additionally, it stimulates mitogenesis and apoptosis of tumor cells. RTKs contain two domains – intracellular

tyrosine kinase domain and extracellular ligand-binding domain. The ligands binding to the IGF-IR activate tyrosine kinases and induce conformational changes.⁹⁴ After activation, antiapoptotic effects of the IGF-IR are mediated via the Akt/PI3K pathways and IGF-IR is overexpressed in many cell types.⁹⁵ RTKs such as IGF-IR and c-erbB-2/HER-2/neu (HER-2/neu) have been reported for the breast cancer cell growth. Inhibition of these RTKs helps in reduction of cell growth and drug development.⁹⁶ Several reports demonstrate the evidence for overexpression and hyperactivation of the IGF-IR in the early stages of breast cancer.^{97–99} The negative expression of IGF-IR, using monoclonal antibodies, antisense IGF-IR, catechols, and transfection methods,

can inhibit the tumor growth in breast cancer.^{100,101} Nordihydroguaiaretic acid is a phenolic compound and is reported as a direct inhibitor of both IGF-IR and the HER-2/neu receptor in breast tumor cells and induces apoptosis. Thus, negative expression of IGF-IR with a potential inhibitor can play an important role in breast cancer therapy.

VEGF

VEGF serves as a primary stimulus of angiogenesis when upregulated by various hormones, cytokines, and transforming growth factors. It is associated with the development, progression, and metastasis of breast cancer, through receptors such as VEGFR-2 (also known as flk/kdr), VEGFR-1 (also known asflt), and VEGF-C (homolog of VEGF gene family). VEGF-2 (flk) and VEGF-1 (flt) are expressed on vascular endothelial or non-endothelial cell-specific receptor;¹⁰² VEGFR-1 (flt) is found on monocytes, whereas VEGF-C receptor (flt-4) is expressed on endothelial cells of lymphatic vessels.¹⁰³ VEGFRs play an important role in the antiapoptotic mechanisms in breast cancer cells.¹⁰⁴ The receptor-based monoclonal antibodies have been reported to inhibit VEGF activity, which downregulates the growth of tumors and their blood vessels.¹⁰⁵ The siRNA as well as anti-VEGF antibody therapy is already in clinical trials for regulation of VEGF activity.¹⁰⁶ Therefore, targeting of endothelial growth factor either alone or in combination with a target agent could be the future therapeutic strategy for metastatic breast cancer.

Conclusion

Drug carrier systems allow for the controlled release of drugs at the desired sites, thus altering the pharmacokinetics and biodistribution of the drugs. In this sense, nanoparticles are intrinsically advantageous over conventional particles. This study provides an overview of all aspects of drug delivery mechanisms using nanocarriers for metastatic breast cancer treatment. Precise drug release into highly specific targets involves miniaturizing the delivery systems to be much smaller than their targets. It is highly expected that these minute drug delivery system can be realized through the advances in nanotechnology. The integration of nanotechnology products, such as nanoparticles, with therapeutic agents, has recently created a new therapeutic trend that would not otherwise be possible.

Acknowledgments

The authors thank Ms Angela Wimes for her critical review of the manuscript. This study was supported in part by the National Cancer Institute of the National Institute of Health

under Award Number SC1CA193758 and by National Institute of Health under Award Number 5G12MD007602.

Disclosure

The authors report no potential conflicts of interest in this work.

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