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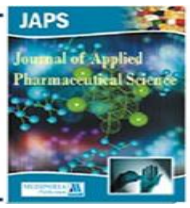

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Nanocarrier-Based Drugs: The Future Promise for Treatment of Breast Cancer

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ABSTRACT

Breast cancer is by far the commonest cancer in women; more than 1 million women world wide are diagnosed with breast cancer every year. Treatment options of breast cancer are surgery, radiation and chemotherapy. Although there have been significant advances in breast cancer treatment over the past several decades, current therapeutic approaches are limited by non-specific systemic distribution, inadequate drug concentrations reaching the tumor and multi-drug resistance.The application of nanotechnology to medicine helps to overcome limitations relating to chemotherapy. Nanoparticles with enhanced surface properties are able to diffuse with greater ease inside the tumor cells delivering a high amount of drug selectively to tumor cells with significant reduced toxicity.In the near future, the use of nanotechnology could revolutionize the entire of breast cancer treatment. The present review examined some of the approved nanocarrier-based drugs for treatment of breast cancer. Also, other drugs under development or in preclinical trials to be used in the near future will be discussed.

Keywords: Breast cancer, anticancer drugs, nanotechnology, nanoparticles, gene therapy.

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INTRODUCTION

The large increase in the number of breast cancer patients is expected in the next few decades, partly as a result of the success in eradicating infectious diseases and maternal deaths. In addition, the life span of women is also increasing and so more women are reaching the age where breast cancer rates are high. The exact causes of breast cancer are largely unknown, but both environmental and genetic factors are involved. Specific mutations in genes known as HER2, BRCA1, BRCA2, CHEK2, and p53 have been linked to breast cancer; these mutations may be inherited or acquired. Mutations that are inherited often substantially increase a person's risk for developing breast cancer (Wooster and Weber, 2003; Nelson *et al.*, 2005). The majority of these cancers could be avoided if appropriate genetic screening and preventive interventions were applied (Agnantis *et al.,* 2004).Other factors, include prolonged exposure to estrogen (Garcia-Closas *et al.*, 2006), use of oral contraceptives, alcohol consumption and previous chest irradiation (John *et al.*, 2007). Women who had certain kinds of benign tumors are also more prone to developing breast cancer (Key *et al.*, 2001). Angiogenesis, the process of new blood vessel formation, plays a central role in both local tumor growth and distant metastasis in breast cancer (Folkman 1971; Jensen *et al.*, 1982). Fibrocystic lesions with the highest vascular density are associated with a greater risk of breast cancer (Guinebretiere *et al.*, 1994).

One of the most critical points in breast cancer treatment is early stage diagnosis, before tumor cells metastasize.In addition current diagnostic and therapeutic approaches rely predominantly on surgery and crude, non-specific techniques such as irradiation and chemotherapeutic agents (Duong and Mousa,2009; Fuller and Thomas, 2010). Unfortunately, cancer therapies are limited by inadequate drug concentrations reaching the tumor.The rapid elimination and widespread distribution of the drug into targeted organs and tissues requires its administration in large quantities which often results in systemic toxicity and adverse effects (Cho *et al*., 2008; Baviskar *et al.*, 2011). Moreover, the majority of anticancer drugs are water insoluble and need to be dissolved in an organic solvent in order to be administered as an injectable solution. These organic solvents are toxic and have their own side effects (Kwon, 2003).

The development of resistance to chemotherapeutic agents is one of the major challenges in effective cancer treatment. Tumor cells are able to generate multi-drug resistance (MDR) to the majority of anti-cancer drugs (Jabr-Milane *et al*., 2008). Resistance to treatment results from a variety of factors including individual variations and somatic cell genetic differences in tumors, even those from the same tissue. The most common reason for acquisition of resistance to a broad range of anticancer drugs is expression of one or more energy-dependent transporters that detect and eject anticancer drugs from cells (Gottesman, 2002).

The application of nanotechnology to medicine (nanomedicine) has the potential to offer solutions to these current obstacles in cancer therapies.The unique size (1-100nm) and large surface-to-volume ratios of nanoparticles (Singh *et al.,* 2008) offer the ability to convert insoluble or poorly soluble drugs into soluble suspensions, thus eliminating the need for toxic organic solvents. The incorporation of anticancer drugs into nanoparticles not only has the potential to decrease their adverse cytotoxic effects, but also increase the accumulation of the drug in the tumor vasculature (Matsumura and Maeda, 1986; Iyer *et al*., 2006; Nam *et al*., 2009). Therefore, cancer nano-therapeutics are rapidly progressing and are being implemented to solve several limitations of conventional drug delivery systems (Liang *et al*., 2010).

Nanoparticles can be engineered to incorporate a wide variety of chemotherapeutic agentsand target the delivery of these agents directly and specifically to the tumor site for better efficacy and less toxicity (Brannon-Peppas and Blanchette, 2004; Wang and Thanou, 2010).Combining types of passive encapsulation and release modalities with surface modifications (i.e. hydrophilic coatings) or tumor-specific targeting moieties could potentially increase the efficacy of nanoparticulate formulations several-folds. In this way, nanoparticles with enhanced surface properties may be able to deliver a high amount of drug selectively to tumor sites (Bharalia and Mousaa, 2010). Obviously, nanoparticles have the ability to accumulate in cells without being recognized by P-glycoprotein (P-gp), one of the main mediators of multidrug resistance, resulting in an increased intracellular concentration of drugs (Cho *et al.,* 2008). Wang *et al.,* (2010) developed an efficient and targeted delivery of antisense oligodeoxynucleotides as ODNs, using folic acid conjugated hydroxypropyl-chitosan. These nanoparticles were designed to reduce production of P-gp, in order to overcome tumor drug resistance.

NANOCARRIER-BASED DRUGS FOR TREATMENT OF BREAST CANCER

In recent years, there's been an explosion of life-saving treatment advances against breast cancer. The most important is the development of nanocarriers that allow tumour-selective delivery of anticancer agents to increase the cell-killing effect and protect healthy cells from exposure to the toxic agent thus reducing the systemic toxic effects. Clinically approved nano-formulations for breast cancer treatment are listed in Table 1.

Table. 1: Examples of nanocarrier-based drugs for treatment of breast cancer on the market.

Compound	Commercial name	Nanocarrier	Indication
Paclitaxel	Abraxane	Albumin-bound paclitaxel Nanoparticles	Metastatic breast cancer
Doxorubicin	Myocet	Liposomes	Recurrent breast cancer
Doxorubicin	Doxil/Caelyx	Pegylated-liposomes	Recurrent breast cancer

Paclitaxel

Paclitaxel (Taxol) is classified as a plant alkaloid used in the treatment of breast, lung, and advanced ovarian cancers (Onetto *et al.,* 1993; Spencer and Faulds, 1994) as well as other types of solid tumers. Paclitaxel as a microtubule inhibitor works by attaching itself to microtubules, which form the framework inside living cells stabilizing them against depolymerization. This will result in inhibition of cell division (Hamel 2003; Mollinedo and Gajate, 2003). One problem with using paclitaxel as a general inhibitor of cell division is that it works on all cells, including healthy cells that tend to divide rapidly.

Regarding metastatic breast cancer (MBC), Holmes *et al.*, (1991) and Reichman *et al.,* (1993) reported that paclitaxel alone provided response rates of approximately 60% in two small series of chemotherapy-naive patients. This response rate was particularly impressive compared with the 43% response rate seen with doxorubicin (Henderson, 1991).Although paclitaxel proved to play a central role in the treatment of MBC, (Romero Acun *et al.,* 1999), its use is limited by its poor solubility and the toxicities associated with Cremophor EL (polyethoxylated castor oil), the lipid-based solvent used as a vehicle for paclitaxel. Polyethylated castor oil contributes to the severe toxicities observed in patients treated with paclitaxel. These include hypersensitivity reactions and peripheral neuropathy (Lorenz *et al.,* 1977; Weiss *et al.,* 1990; Gelderblom *et al.,* 2001). Also, the administration of paclitaxel requires a large volume of IV fluid, a long infusion period (up to 24 hours), special IV-infusion sets, in-line filters, and premedication with steroids and antihistamines to minimize the risk of hypersensitivity reactions (Lorenz *et al.,* 1977; Kloover *et al.,* 2004; Winer *et al.,* 2004). In addition, polyethoxylated castor oil forms micelles in the plasma compartment that entrap

paclitaxel, resulting in nonlinear pharmacokinetics and lack of dose-dependent antitumor activity for paclitaxel (van Tellingen *et al*., 1999). Therefore, several studies were carried out to deliver more of the drug to cancer cells and to reduce its side effects. Sharma *et al*., (1996) were the first to report the development of a nanoparticulate paclitaxel formulation using polyvinylpyrrolidone nanoparticles. Since then, Fonseca *et al*., (2002) showed that biodegradable nanoparticles consisting of poly (lactide-co-glycolide) (PLGA)-based polymers exhibited an initial fast release during the first 24 h of administration, followed by a slower continuous release phase.Dong and Feng (2005) reported that oral formulation of paclitaxel using PLGA/montmorillonite (PLGA/MMT) nanoparticles exhibited enhanced uptake efficiency for PLGA/MMT versus PLGA nanoparticles by 11–55% for HT-29 cells. This formulation has the potential to offer longer residence time in the gastrointestinal tract, and hence may provide an efficient mechanism for the oral delivery of paclitaxel. Sun et al. (2008) highlighted the potential of PLGA/MMT nanoparticles in targeted breast cancer therapy. PLGA/MMT nanoparticles incorporating paclitaxel with the anti-human epidermal growth factor receptor-2 (HER2) antibody "trastuzumb" showed a significantly higher level of uptake of anti-HER2-conjugated PLGA/ MMT nanoparticles as compared to unconjugated nanoparticles in SK-BR-3 breast cancer cells. In 2005, the FDA approved Abraxane for the treatment of breast cancer. ABI-007 (Abraxane; American BioScienceInc, Santa Monica, CA) is a castor oil–free, albumin-bound paclitaxel. It is the first of a new class of anticancer agents that incorporate albumin, a natural carrier of lipophilic molecules in humans (Zamboni, 2008; Fu *et al*., 2009).Gradishar *et al*., 2005 reported that ABI-007 compared with the current standard of solvent-based paclitaxel, demonstrated significantly higher response and significantly longer time to tumor progression. The incidence of grade 4 neutropenia was significantly lower for ABI-007 compared with standard paclitaxel despite a 49% higher paclitaxel dose. On the other hand, the authors reported that, Grade 3 sensory neuropathy was more common in the ABI-007 arm than in the standard paclitaxel arm but was easily managed and improved rapidly. No hypersensitivity reactions occurred with ABI-007 despite the absence of premedication and shorter administration time. The authors concluded that the superior efficacy, favorable safety profile, and greater patient convenience of ABI-007 make it an important advance in the treatment of patients with MBC.

Human serum albumin stabilizes the drug particle at an average size of 130 nm which prevents any risk of capillary obstruction and does not necessitate any particular infusion systems or steroid/antihistamine premedication before the infusion (Desai *et al.,* 2006)resulting in a significant antitumor activity in patients with MBC, including those receiving the drug as first-line therapy (Ibrahim *et al*., 2005).In addition, albumin has the potential to enhance drug transport into tumors by taking advantage of albumin receptor-mediated transcytosis across endothelial cells (John *et al*., 2003). For these reasons, Abraxane is highly recommended after failure of combination chemotherapy for metastatic disease or relapse within six months of adjuvant chemotherapy (Cortes and Saura, 2010). Synthesis of nanoparticles using combinations of different polymers, or hybrid polymers confer additional flexibility in terms of loading drugs of different solubility. Hybrid targeted polymeric nanoparticles incorporating paclitaxel were reported by Pan and Feng (2008). One component was poly(lactide)–D-α-tocopheryl polyethylene glycol succinate (PLA–TPGS) for hydrophobic–lipophilic balance, and the second was TPGS–COOH, which facilitated conjugation of the targeting moiety folate. The hybrid nanoparticles achieved better therapeutic efficacy as compared to free paclitaxel by 8.68% for MCF-7 breast cancer cells, and conjugation of folate enhanced the delivery of the drug into cancer cells and the therapeutic effects of paclitaxel.

Gold nanoparticles possess a unique combination of properties which allow them to act as highly multifunctional anti-cancer agents. Gold nanoparticles are used for both detecting and destroying cancer cells as they can carry chemicals to destroy a cancer cell or they can be used with radiation. Taking gold nanoparticles to the cancer cell and hitting them with a laser has been shown to be a promising tool in fighting cancer.The heated nanoparticles would in turn heat the cancer cell up which would destroy the cancer cell without harming healthy cells. Using gold nanoparticles, Gibson *et al*., (2007) have discovered a way to load dozens of molecules of paclitaxel onto tiny gold spheres that is barely wider than a strand of DNA without chemically altering the drug. Eghtedari *et al.,* (2009) described a novel technique to functionalize gold nanorods (GNRs) allowing for in- vivo targeting of breast cancer tumors grown in athymic nude mice. GNRs were functionalized by covalent attachment of Herceptin (HER), a monoclonal antibody that enables molecular recognition of breast cancer cells expressing highly specific tumor associated antigens, and poly(ethylene glycol) (PEG) which obscures particles against the reticuloendothelial system in the body (Figure1). The stability and functionality of fabricated particles (Her-PEG GNRs) were demonstrated in vitro in the presence of blood and then in vivo in nude mice model for breast cancer.

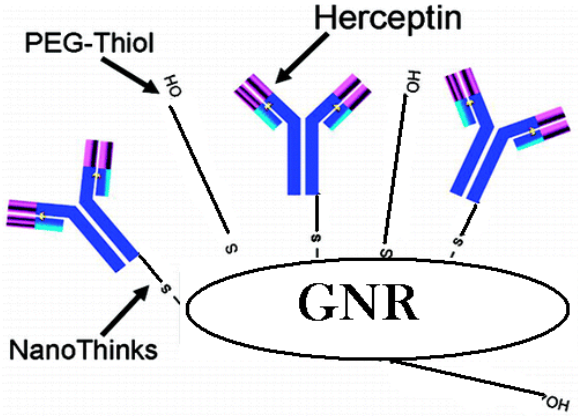

Fig. 1: Schematic representation of Herceptin- poly(ethylene glycol) gold nanorods (Her-PEG GNRs).

Doxorubicin

One of the most powerful and widely used anticancer drugs is doxorubicin. It is an anthracycline antibiotic that binds to DNA preventing DNA double helix from resealing, thus effectively halting replication through blocking the activity of topoisomerase II enzyme that essentially unwinds the DNA helix for replication. Doxorubicin, plays an important role in the treatment of breast cancer, both in the adjuvant and metastatic settings. However, the benefits of conventional doxorubicin activity are limited by many of its side-effects like cardiotoxicity and bone marrow depression (O'Shaughnessy, 2003). Much effort has been made to target doxorubicin to cancer tissues to improve its efficacy and to decrease many of its side-effects. Three liposomal anthracyclines, all of which are nanoparticles measuring about 100 nm, are being assessed in human cancers: liposomal daunorubicin for the treatment of Kaposi's sarcoma; liposomal doxorubicin, which, in combination with cyclophosphamide, is approved for the treatment of MBC; and pegylated liposomal doxorubicin, approved for both Kaposi's sarcoma and refractory ovarian cancer (Batist *et al.,* 2001; O ' Brien *et al.,* 2004). Both liposomal doxorubicin and pegylated liposomal doxorubicin have been compared with conventional doxorubicin in first-line treatment of patients with MBC. O'Shaughnessy (2003) reported that pegylated liposomal doxorubicin provides tumor-targeted efficacy without many of the toxicities associated with conventional doxorubicin, including myelosuppression, alopecia, nausea and vomiting, and most importantly, cardiac toxicity. As a single agent, pegylated liposomal doxorubicin has demonstrated similar efficacy to that of conventional doxorubicin in patients with MBC. It has also demonstrated efficacy in combination with other agents or modalities, including cyclophosphamide, paclitaxel, docetaxel, gemcitabine, vinorelbine, and hyperthermia. Several studies reported that sustained-release liposomal formulation of doxorubicin treatment of MBC has demonstrated significantly improved efficacy as compared to free doxorubicin (Martin, 1998; Park, 2002; NishiyamaandKataoka, 2006).

Drug resistance can be mediated by a number of different mechanisms. In case of doxorubicin, it may be due to an increase in the activity of ATP-dependent efflux pumps resulting in reduced intracellular drug concentrations (Ambudkar *et al.,* 1999). Different types of nanoparticles have been developed to reverse P-gp mediated multidrug resistance of cancer cells to doxorubicin. P-gpmediated multidrug resistance (MDR) is overcome with conventional poly(cyanoacrylate) doxorubicin-loaded nanospheres due to the adsorption of nanoparticles to the cell surface and the increased diffusion of doxorubicin across the plasma membrane. The formation of a complex between positively charged doxorubicin and negatively charged polymer degradation products seemed to favor the diffusion across the plasma membrane (de Verdiere *et al.,* 1997). The association of doxorubicin with poly (alkyl cyanoacrylate) nanoparticles also reversed the resistance to doxorubicin in numerous MDR cell lines (Soma et al.,1999). Furthermore, Laurand *et al.,* (2004) reported that doxorubicin encapsulated in poly (isohexyl cyanoacrylate) nanospheres can circumvent P-gp mediated MDR. MCF7 cell lines, from human breast adenocarcinoma were more resistant to free doxorubicin than to doxorubicin poly-(isohexyl cyanoacrylate) nanospheres. Also, doxorubicin was complexed with a new soybean-oil-based anionic polymer and dispersed together with a lipid in water to form doxorubicin -loaded solid lipid nanoparticles (SLNs). Treatment of MDR human breast cancer cells with doxorubicin–SLN resulted in over 8-fold increase in cell kill when compared to doxorubicin solution treatment at equivalent doses (Wong *et al.,* 2006). Doxorubicin (SLN) was studied in in P-gp over-expressing MCF-7/ADR cells, a representative doxorubicin-resistant breast cancer cell line. SLNs did not show hemolytic activity in human erythrocytes. In comparison with doxorubicin, SLN-doxorubicin efficiently enhanced apoptotic cell death through the higher accumulation of doxorubicin in MCF-7/ADR cells. Therefore, doxorubicin-SLN have potential to serve as a useful therapeutic approach to overcome the doxorubicin-resistant breast cancer (Kang *et al.,* 2010).

Tamoxifen

Tamoxifen is a nonsteroidal anti-estrogen drug commonly used to treat breast cancer in women and men for more than three decades. Tamoxifen is classified as a selective estrogen receptor modulator (MacGregor and Jordan, 1998; Jordan, 1999). Tamoxifen fits into the estrogen receptor and blocks estrogen from reaching the cancer cells so it alters cancer growth, subsequently initiating programmed cell death. Tamoxifen also decreases the chance of recurrence in some early-stage breast cancers and prevents the development of cancer in the opposite breast. Oral administration of tamoxifen is today the endocrine treatment of choice for patients with all stages of estrogen receptor positive breast cancer (Lerner and Jordan, 1990). Tamoxifen is also thought to induce a tumoricidal effect on estrogen receptor-negative cells by increasing the secretion of inhibitory growth factors such as TGFβ (MacGregor and Jordan, 1998; Jordan, 1999). Also, it was reported that tamoxifen may possess anti-angiogenic activity through its anti-estrogenic effects (Ruohola *et al.,* 1999). Following long-term therapy, tamoxifen has some major side effects, including higher incidence of endometrial cancer, liver cancer, thromboembolic disorders, and development of drug resistance (Jordan, 1995). Tamoxifen resistance has been shown in a variety of cells in vitro as well as in vivo (Johnston, 1997).To increase the local concentration of tamoxifen in estrogen receptor-positive breast cancer cells, poly (ε-caprolactone) nanoparticles labeled with rhodamine 123 were incubated with MCF-7 estrogen receptor-positive breast cancer cells. A significant fraction of the administered rhodamine 123-loaded poly (ε-caprolactone) nanoparticles was found in the perinuclear region of the MCF-7 cells, where estrogen receptors are localized. These nanoparticles were rapidly internalized in MCF-7 cells and intracellular tamoxifen concentrations followed a saturable process (Chawlaand Amiji, 2003). In another study, Shenoy and Amiji (2005) studied the biodistribution profile of tamoxifen-loaded polyethylene oxide-modified poly (ε-caprolactone) nanoparticles in athymic mice

bearing a human breast carcinoma xenograft, using tritiated [3H]tamoxifen as radio-marker for quantification. After intravenous administration, the drug loaded nanoparticles accumulated primarily in the liver. In comparison with free drug and uncoated nanoparticles, the modified nanoparticles exhibited a significantly increased level of accumulation of the drug within the tumor with time as well as prolonged drug presence in the systemic circulation.Once accumulated within the tumor interstitium by exploiting vascular abnormalities that allows free access to the tumor mass, the nanoparticle system would increase the drug concentration inside the tumor cells as a result of non-specific endocytic process, followed by gradual release of the drug (Chawla and Amiji, 2003). Such nanoparticle-mediated intracellular delivery is particularly beneficial for tamoxifen therapy as the estrogen receptors are in the cytosol and nucleus (Shenoy and Amiji, 2005). Solid lipid nanoparticles (SLNs) have recently received considerable attention as alternative drug delivery carrier. Alhaj *et al.* (2008) studied the anti-proliferative activity of SLNs containing tamoxifen against MCF-7 cells. They demonstrated that tamoxifen loaded SLN showed a significant cytotoxicity against MCF-7 cells and may be considered as an alternative formulation for tamoxifem for breast cancer therapy. Dreaden *et al.* (2009) synthesized a thiol-Poly ethylene glycol (PEG)tamoxifen derivative that can be used to selectively target and deliver plasmonic gold nanoparticles to estrogen receptor positive breast cancer cells with up to 2.7-fold enhanced drug potency in vitro. The augmented activity was due to increased rates of intracellular tamoxifen transport by nanoparticle endocytosis, rather than by passive diffusion of the free drug. Recently, Ostad *et al.* (2010) investigated the cytotoxicity of silver ions (Ag+) and silver nanoparticles (Ag NPs) in both parent and tamoxifen-resistant T47D human breast cancer cell lines. They demonstrated that at non-cytotoxic concentrations ofAg+, Ag NPs, and tamoxifen, the combination of Ag+-tamoxifen and Ag NPs-tamoxifen is still cytotoxic to tamoxifen-resistance cells suggesting that much lower doses of tamoxifen may produce the same cytotoxic effect with less undesirable side effects.

Cisplatin

Cisplatin is one of the most widely used antineoplastic alkylating agents for the treatment of certain cancers such as testicular, breast, ovarian cancers,and many other malignancies (Kostova, 2006). Cisplatin is a DNA cross linking agent that interferes with mitosis and triggers apoptosis or cell death. It's effectiveness lies in how easily it releases its platinum molecule to cross-link DNA strands, which in turn disrupts cell division (Cepeda *et al.*, 2007). The principal limitations for cisplatin use are due to its possible severe toxicities; nephrotoxicity, neuropathy, ototoxicity, and hematological toxicities. The most important significant toxicity is linked to renal damage (Paraskar *et al.*, 2011). The coupling of nanotechnology and structure-activity relationship to rationally reengineer cisplatin could have a major impact globally in the clinical treatment of cancer (Paraskar *et al.*, 2010). Boulikas (2009) developed a method of reducing therapeutic difficulties associated with cisplatin by encapsulating cisplatin into liposomes having a different lipid composition between the inner and outer membrane bilayers enabling cisplatin to reach primary tumors and their metastases after intravenous injection. Therapeutic efficacy was determined utilizing a human breast carcinoma MCF-7 bearing murine model. Significant tumor regression occurred after intravenous injections of the liposome encapsulated cisplatin. Later on, Paraskar et al. (2010) engineered a novel polymer, glucosamine-functionalized polyisobutylene-maleic acid, where platinum can be complexed to the monomeric units. This complex self-assembles into a nanoparticle, which releases cisplatin in a pH-dependent manner. The nanoparticles exhibited improved antitumor efficacy in terms of tumor growth delay in breast cancer model cancers. Furthermore, the nanoparticle treatment resulted in reduced systemic and renal toxicity, validated by decreased distribution of platinum to the kidney. Lipoplatin is a liposomal cisplatin encapsulated into liposome nanoparticles of an average diameter of 110 nm developed in order to reduce the systemic toxicity of cisplatin. Also, preclinical trials have demonstrated the ability of this molecule to be concentrated up to 50 times more in malignant tissues than in normal tissues (Stathopoulos and Boulikas, 2005). Lipoplatin has substantially reduced the renal toxicity, peripheral neuropathy, ototoxicity, myelotoxicity as well as nausea/vomiting and asthenia of cisplatin in Phase I, II and III clinical studies with enhanced or similar efficacy to cisplatin (Boulikas, 2009)

Fluorouracil

Fluorouracil (5-FU) is an anticancer agent widely used in the treatment of malignancies arising from breast, gastrointestinal tract, head, and neck regions of the body for several decades (Schmoll *et al.*, 1999).5-FU is a pyrimidine analog that acts in several ways, but mainly as a thymidylate synthase inhibitor. Interrupting the action of this enzyme blocks synthesis of thymidine, which is a nucleotide required for DNA replication (Longley *et al.*, 2003). 5-FU can be used in combination with other chemotherapy drugs to treat any stage of breast cancer. It was found that addition of 5-FU to doxorubicin-paclitaxel sequence increases caspase-dependent apoptosis in breast cancer cell lines (Zoli *et al.*, 2005). Also, it is sometimes used in the treatment of inflammatory breast cancer, an aggressive form of breast cancer (Cristofanilli *et al.*, 2003). Recently, Nair *et al.*, (2011) evaluated the antitumor efficacy of 5-fluorouracil (5-FU)-entrapped poly (D, L-lactic-co-glycolic acid) (PLGA) nanoparticles in breast adenocarcinoma (MCF7) cell lines. In vitro release studies showed the prolonged and sustained release of 5-FU from nanoparticles. Nanoparticles with PLGA combination exhibited better cytotoxicity than free drug in a dose- and time-dependent manner against the tumor cell lines.

Gene therapy

Gene therapy is a method used to stimulate the body'simmune response to attack cancer cells by introducing genetic material; DNA or RNA to activate cellular processes for

reducing or eliminating disease (Praetorius and Mandal, 2007). Nanoparticle-based DNA and RNA delivery systems offer several potential advantages for gene delivery to various human tumours, including breast cancer. DNA molecules are encapsulated into the nanoparticle and are thus protected from degradation. In addition, conjugation of a polyethylene glycol molecule to the surface of the nanoparticle with targeted antibody increases gene delivery into tumour cells.Hayes et al. (2006) have used this method to allow gene delivery to human ERBB2-positive breast-cancer cells using a ERBB2-directed antibody conjugated to a nanoparticle.

Major strategies in breast-cancer gene therapy include transfer of tumour-suppressor genes, enhancement of immunological response, transfer of suicide genes, and bone-marrow protection by use of drug-resistance genes (Takahashi *et al*., 2006). Breast-cancer genome abnormalities for which gene therapy could be potentially useful include amplification or mutation of multiple genes, including ERBB2, P53, MYC, and cyclin D1 (Osborne *et al.*, 2004).Hortobagyiet al. (2001) has shown successful transfer of E1Agene complexed with cationic liposome to human breast and ovarian cancers. Patients with breast or ovarian cancer (ERBB2-positive or low ERBB2 expressing) were treated in a phase I trial with this cationic liposome-mediated E1A gene-transfer system, E1A gene expression in tumour cells suggesting successful gene transfer. Prahba and Labhasetwar (2004) showed anti-proliferative activity of wild-type P53-loaded nanoparticles in a breast-cancer cell line. Nanoparticles containing plasmid DNA using a biocompatible polymer, poly (D,L-lactide-co-glycolide). Cells transfected with wild type P53 DNA-loaded nanoparticles showed significantly greater anti-proliferative effect than did those with naked wildtype P53 DNA, resulting in anti-proliferative activity, which could be therapeutically beneficial in breast-cancer treatment.

CONCLUSIONS

Among the major challenges in effective breast cancer chemotherapies are inadequate drug concentrations reaching the tumor, their rapid elimination, systemic toxicity and adverse effects.Nanotechnology has the potential to overcome current chemotherapeutic barriers in breast cancer treatment and to solve the problems associated with traditional chemotherapy and multidrug resistance. In view of previous observation, conjugation of different anticaner drugs with nanoparticles will be highly promising agent for breast cancer treatment with less side effects, low doses of the prescribed drug and to overcome drug resistance by tumor cell. This will increase the efficacy of the drug and maximize patient compliance, while enhancing the ability to use highly toxic, poorly soluble, or relatively unstable drugs. The application of nanotechnology could save a patient from months of ineffective medication and debilitating side effects, allowing a switch to a potentially more effective course of treatment. Unfortunately, there are only a few clinically approved nanocarriers drugs that selectively target breast cancer cells. Abraxane, the albumin-bound form of paclitaxel in the nanoparticlestate, allows infusion of significantly higher doses of paclitaxel without premedication, resulting in a significant antitumor activity in patients with MBC. Also, the pegylated liposomal doxorubicin provides tumor-targeted efficacy without many of the toxicities associated with conventional doxorubicin in treatment of MBC. We hope that in the near future, we witness the development of a new generation of other nanocarrier anticancer drugs (tamoxifen, cisplatin, fluorouracil and others) for more effective breast cancer therapies.

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