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Targeting nanoparticles for breast cancer

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Abstract
Breast cancer is the second most cause of cancer death in case of women. It is the major issue among women of both old and young age. Efforts have been made by clinicians and researchers to improve the breast cancer treatment because the traditional approaches have low specificity and some side effects. Nanotechnology is a hopeful way for breast cancer treatment. It is rapidly emerging field which provides a big platform for the diagnosis and treatment of cancer. The use of nanoparticles enhanced the circulation time and accumulation of drugs in tumor. Nanoparticles mediated drug delivery provides high stability, less toxicity and more loading capacity as compare to traditional chemotherapeutic drugs. In this chapter we will summarize the most recent therapeutic nanoparticle mediated Drug Delivery Systems (DDS) and their significance in breast cancer treatment.

Keywords: breast cancer, drug delivery systems, nanoparticles

Introduction
Cancer is a group of disease causing cells in the body to change and proliferate beyond the control. Most types of cancer cells eventually form a lump or mass called tumor and they named after the part of body where they originates. Breast cancer is the most common cause of cancer-related deaths in women and occurs most frequently in postmenopausal women over the age of 50. Breast cancer is very rare, making up to 1% of all the breast cancer cases. Globally, it is the leading cancer in terms of the number of new cases; approximately 2.1 million diagnoses were estimated in 2018, contributing about 11.6% of total cancer burden out of that 627,000 deaths were reported, which accounts for 15% of all the cancer deaths. In India, among females, breast cancer is the most commonly diagnosed cancer (27.7%) and is the leading cause of death (23.5%). The burden of breast cancer is growing at a worrying rate in India. Breast cancer is the cancer, which forms in the tissues of breast usually in the ducts or lobules. A duct carries milk to the nipple and lobules are the gland that makes milk(Hashim, 2015) [11]. It has been seen that most lumps are benign (non-cancerous), which do not spread. Mostly Invasive Ductal carcinoma has been observed in females but in young females inflammatory breast cancer is more common. They are more commonly classified on the basis of pathological classification they can be- Non-invasive, Invasive and Metastatic breast cancer, Which according to TNM classification forms stages (0-1), (2-3) and 4 respectively. Metastatic breast cancer is the late stage of cancer, which has been spread to the distant organs like lungs, liver or brain. It is the main cause of death. Approximately 30% of all the women suffering from breast cancer develop metastasis. In addition breast cancer is also classified on the basis of its molecular subtypes including luminal A, luminal B, HER-2 type and Triple Negative breast cancer (TNBC) (Provenzano, Ulaner and Chin, 2018) [30].

Traditional treatment includes- Surgery (mastectomy and lumpectomy), Radiotherapy and Chemotherapy. The major drawbacks of these therapies are their low specificity as well as side effects of these therapies were also reported. Chemotherapy may lead to cardiac dysfunction and radiotherapy can damage the neighboring healthy tissues. Nanotechnology being an emerging field motivates the development of targeted therapy for the treatment and diagnosis of breast cancer. Nanoparticles have the ability to alter the biological processes, for example infections. Nanoparticles based drug delivery system provides many benefits they have high capacity, low toxicity, small size, more stability, more feasible due to active and passive targeting and there can be various route of administration including oral as well as inhalation (Kester and Meyers, 2017) [16]. Nanoparticle based targeted therapy includes Organic drug delivery approaches, Inorganic drug delivery approaches, Localized drug delivery and Receptor based drug delivery. Side effects of traditional treatments can be overcome by the nanoparticles. Therefore development of new targeted therapy by the combination of various therapeutics we can achieve a better outcome as compare to traditional therapy used for the treatment of breast cancer (Liyanage *et al.*, 2019) [20].

Traditional Drugs and Breast Cancer Biomarkers
Chemotherapeutic drugs and their side effects
We are aware about the adverse effects of cancer therapies. Chemotherapeutic drugs and monoclonal antibody against specific receptors sometime shows cardio toxic effects because these agents target the tumor microenvironment also. A Cardiotoxic effect mostly occurs due to mitochondrial dysfunctoning. Chemotherapeutic drugs include Doxorubicin (Dox), Paclitaxel (PTX), Tomoxifen, Trastuzumab, Cisplatin, Docetaxel (Liyanage *et al.*, 2019)

[20].

Dox is most commonly prescribed for the cancer treatment. It's a member of anthracycline class. For the treatment of breast cancer it can be used alone or in combination with other drugs. The major drawback of Dox is the oxidative mechanism induced by it, which lead to cardiotoxicity and hematopoiesis. Paclitaxel is an important drug for the treatment of breast cancer. It inhibits the dipolymerization of microtubule to achieve anti tumor effects. Neutropenia is the major side effect cause by paclitaxel (Perez, 1998) [29]. On the other hand for all the chemotherapeutic drugs most commonly seen side effects are nausea, weight loss, hair loss, fatigue, heart problems, osteoporosis, decrease in mental functioning, fertility issues in women and nerve damage. So, it becomes important to use alternative of chemotherapy that is Targeted therapy.

Biomarkers in Breast cancer

Biomarkers are the indicator of understanding the disease and biological process from outside the patient. These can be used clinically for the treatment and diagnosis purposes. For nanoparticle mediated drug delivery in breast cancer treatment it's important to study the biomarkers to achieve success in Biomarkers targeted drug delivery. It will target the drug towards cancer cells only (Barzaman *et al.*, 2020) [3]. The most common biomarkers include Estrogen receptor (ER), Progesterone receptor (PR), HER-2 (Human epidermal growth factor receptor). 15% of tumors are TNBC that do not express ER, PR and HER-2. TNBC are most challenging tumors. Monoclonal antibodies as well as drugs can be used to target biomarkers for the treatment of breast cancer.

ER

This receptor is located on the cell membrane as well as inside the cell. Majority of the breast tumors are ER positive. For such type of tumors Tamoxifen is the best drug but this drug do not taret adipose tissue specifically. So, by the use of nanocarriers this problem can be solved. Nanoparticles can enhance the role of tamoxifen (Duffy *et al.*, 2017) [7].

PR

It is a steroid hormone receptor which is used to detect invasive breast cancer. Two forms of PR- PRA and PRB are seen in breast cancer. For all the stages of breast cancer it acts as a prediction marker.

HER-2

It is a type of transmembrane glycogen protein; this family has 4 proteins HER1, HER2, HER3, and HER4. Monoclonal antibodies Trastuzumab (Herceptin) is given in addition to chemotherapy to improve the survival of patients with breast cancer (Guide and Article, 2020) [9].

TNBC

This type of tumor does not express ER, PR and HER-2. This type of tumor is more aggressive and more lethal. 85% of TNBC are basal type. Nanoparticles are used to target the receptors present on the basal like tumor. Delivery of combination of various therapeutic agents gives sufficient results for the treatment of breast cancer.

Targeting Delivery by Nanoparticles

As the tumor cells or tissue increase in size there will be increase demand of oxygen and nutrients to the tissue. To overcome this demand new blood vessels are developed (poorly developed), due to this poor development it become permeable to particles up to certain size. So, the nanoparticles can only enter into tumor tissues due to differences in the characteristics of blood vessels (Hashim, 2015) [11].

Ideally the anticancer drug must follow two things - firstly, it must be able to reach the desired tumor tissues or cells by crossing the different barriers present in the body. Secondly, after reaching to the tumor tissue, it will selectively kill cancerous cells or tissues, not healthy cells. These two strategies can lead to improvement in the treatment of cancer as well as increase the survival of patient. Targeting drug delivery system can be of two types- Passive delivery and Active delivery (Cho *et al.*, 2008) [5].

Passive Delivery

This type of targeting can differentiate into normal and tumor tissues. Drug is targeted in inactive form by passive delivery and it become highly active when it reaches the tumor tissue. Nanoparticles show two types of effect for such delivery- ERS (Enhanced Retention System) and EPS (Enhanced Permeation System) these two collectively called as EPR.

This EPR based targeting is influenced by the size and the time. Size is an important factor but due to fenestration in blood vessels it is limited i.e. 200-800nm sized nanoparticles can only be targeted. The optimal size to target nanomedicine is 20-200 nm. The nanoparticles can only reaches to the tumor tissue if it avoids the renal clearance and RCS. Minimum six hours circulation of drug is required to invade into a specific tissue by EPR effect (fig.1). So, due to this sometime it become unsuccessful.

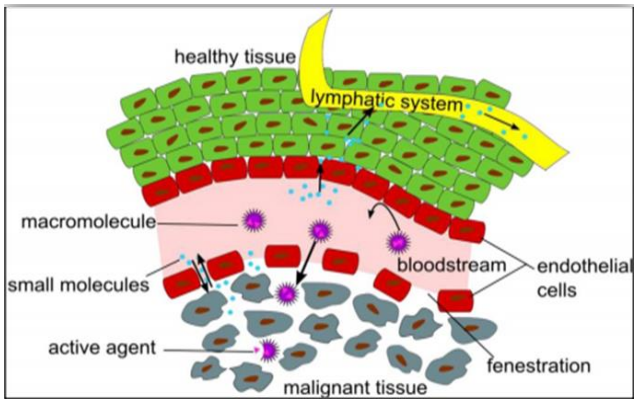

Fig 1: Epr effect of nanoparticle (macromolecule) in malignant tissue (Pardhiya and Paulraj, 2016) [25].

Passive targeting is further classified into three types-

- Leaky Vasculature- It enhances the permeation and retention time by using polymer based nanoparticles.
- Tumor microenvironment- It will only targets the cancerous cells.
- Local Drug Application- If the chemotherapeutic drug is targeted directly to the tumor site, it will increase the drug concentration at the tumor site as well as decrease the systemic toxicity (Sinha, Kim and Nie, 2006) [35].

Active Delivery

To overcome the challenges of passive delivery is to attach affinity ligands like antibody, peptide or any small molecules that will only binds to the specific receptors present on the cell surface (Bamrungsap *et al.*, 2012) [1]. Active targeting will increase the retention time of a drug in tumor tissue. Due to this therapy the affinity of ligand towards receptor will increase the permeation of nanoparticles in tumor tissue. This type of delivery has ability to differentiate between normal and tumor tissue. For example, Herceptin targeted nanoparticles can differentiate between HER-2 positive or HER-2 negative breast cancer. This approach is based upon the specific interactions like- Antibody-Antigen, ligand-receptor, lectin-carbohydrate (fig.2) (Sinha, Kim and Nie, 2006) [35].

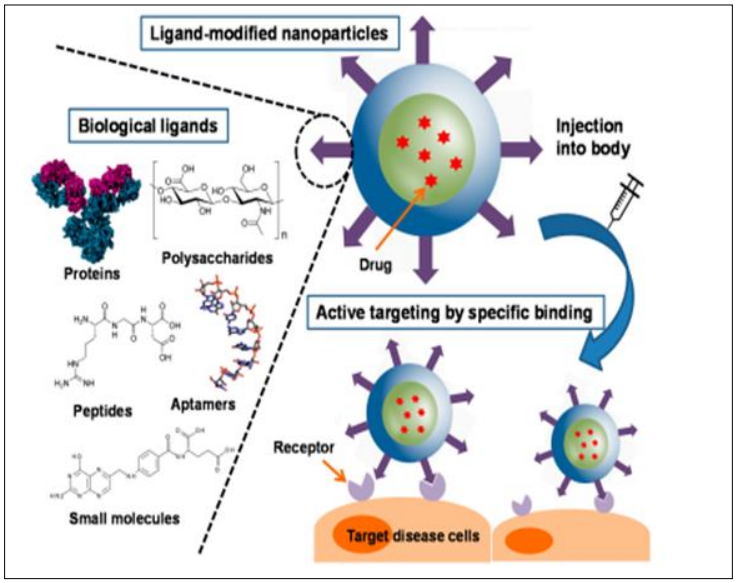

Fig 2: Biological Ligands For Active Targeting Of Nanoparticle Drug Carriers (Yoo *et al.*, 2019) [41].

- Carbohydrate Directed Targeting- It is an excellent example of this approach. Carbohydrate is present on the surface of the cell both normal and tumor. Lectin has an affinity towards glycoprotein. So, lectin can bind to carbohydrateand can be used for the targeting. Similarly, lectin can also be used to target the carbohydrates present on tumor cell surface (Reverse lectin targeting) (Gorelik, Galili and Raz, 2002) [8].
- Receptor targeting- Here the process of endocytosis is applied to achieve active targeting. Drug is being conjugated to a polymer (carrier). This carrier localized on the cell surface when the drug-polymer conjugate invades the tumor intracellular environment drug gets dissociate from the polymer (Kato *et al.*, 1996) [15].
- Antibody Targeting- Kirpotin el al, described the evidence that the monoclonal antibody can be used as a targeting nanoparticle. In his experiment he targets monoclonal antibody towards HER-2 cancer. The nanoparticle for the same was prepared by conjugating anti-HER-2 monoclonal antibody fragments with liposomal grafted polyethylene glycol chain (Kirpotin *et al.*, 2006) [18].

Nanoparticles Delivery system and their Application

- **Drug Delivery Systems**

Nanoparticles based drug delivery system is considered very effective for breast cancer treatment. Nanoparticle improves the effectiveness of drugs by decreasing its toxicity. Drug delivery system targets the tumor site directly hence, reduce the killing of healthy cells.

Nanocapsules are designed in such a way that they have cavity inside which is surrounded by membrane (usually of polymer). Sometimes drug is dispersed in a matrix known as Nanosphere. Nanoparticles (colloidal particles) are made up of macromolecules. They vary in size from 10 nm to 100 nm. The optimal size for anticancer drug deliver in breast cancer is 20-200 nm. Based on the treatment's requirement nanoparticles, nanocapsules or nanospheres are designed. Drug is either attached, absorbed, entrapped, dissolved or encapsulated. This system shows best outcomes in treatment of breast cancer (Barratt, 2000) [2].

- **Applications and Advantage of Nanoparticles**

Nanoparticles can be made easily with the help of natural or synthetic polymers. Nanoparticles seek more attention due to its stability. The release of drug can be controlled by nanoparticles. It has been observed that nanoparticles become highly active after coming in contact with the tumor environment or inflammatory sites of the body due to enhanced EPR effect. Once the nanocarrier reaches the tumor site the nanocarrier continuously supply the drug/therapeutic compound at the disease site i.e. solid tumor (Singh and Lillard, 2009) [34] (Haq *et al.*, 2009) [10].

There are several advantages of using nanoparticles over any other therapy for the treatment of breast cancer. There is no side effect of drug and no surgical treatment is needed, highly specific and sensitive, cost effective, reduced rate of morbidity and mortality rate of breast cancer. Nanoparticles are polymer based; biodegradable and they protect the therapeutic drug from the action of enzymes like – protease and nuclease.

The major advantages of using nanocarriers are its size and they are biodegradable. Due to its small size it can penetrate anywhere in tumors, epithelium, endothelium in tumor sites. Nanoparticles have less than 1micrometer of diameter. Over a period of days drug can be release at the target site. To target intracellular sites PLGA and PLA have been developed for a specific delivery (Patel, Mistri and

Prajapati, 2012) [27].

Selection criteria for a nanoparticle based therapeutic platforms

As the nanotechnology is rapidly emerging so many nanoparticles have been invented for the treatment of breast cancer, but a few of them meet the requirement of US FDA. The major advantage of using nanoparticle is that they are biodegradable and non-toxic (Kester and Meyers, 2017) [16].

Over 240 nanoparticles have been screened; the researchers of National Cancer Institute concluded that, it is difficult to find out the material which is worth satisfying all the criteria. Because some materials may found in nature but, mostly we have to synthesize in laboratory (Hong, 2018) [13]. The nanoparticles can be of various sizes, shape, surface characteristics (fig.3). It can allow the attachment of various ligands, antibodies, peptides etc. Different chemical agents can also be conjugated to enhance the EPR effect.

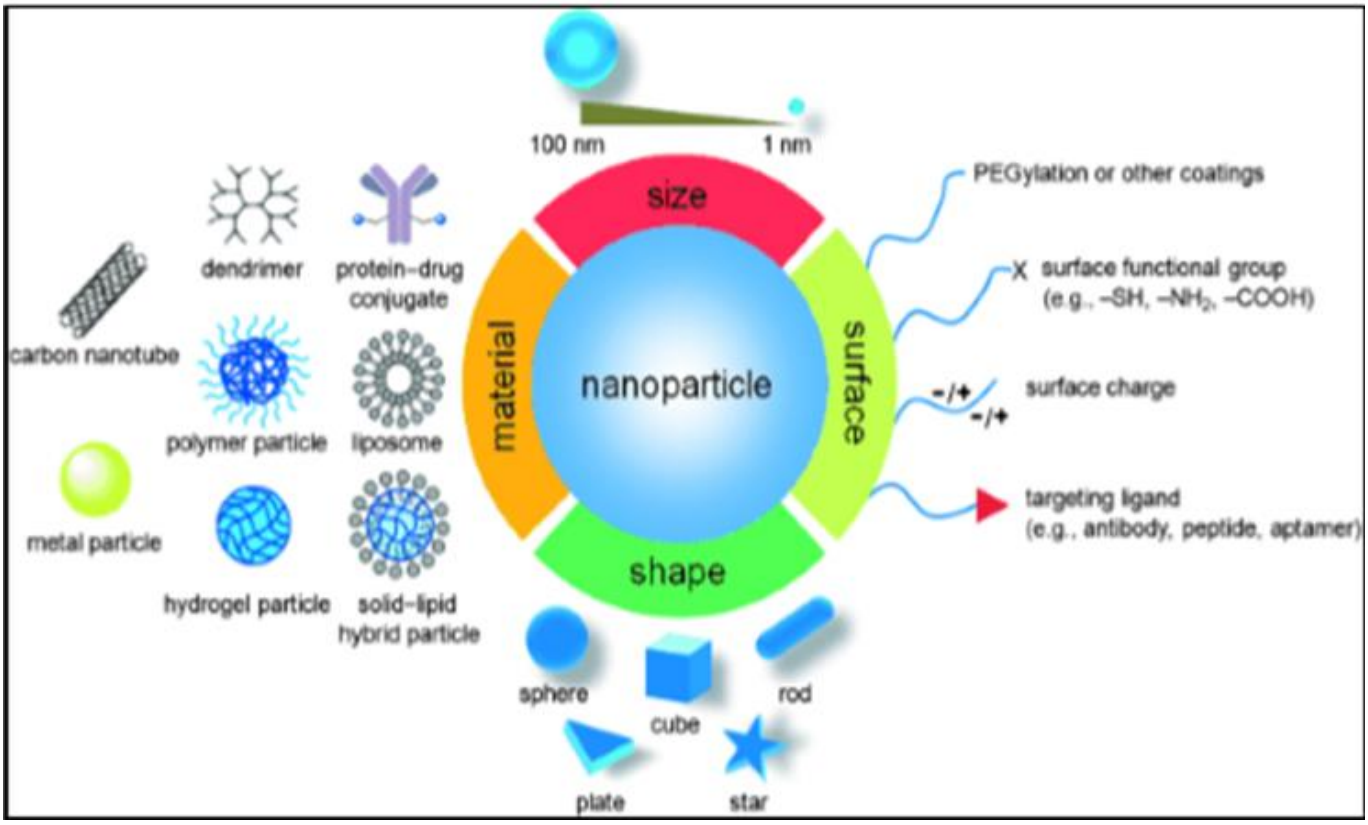

Fig 3: Different Types Of Nanomaterial With Varying Shape, Size And Surface Functions (Pardhiya and Paulraj, 2016) [25].

Desired Characteristics for nanoparticles-

- Nontoxic and Biostable material- Material selection is important because it aims toward human health.
- Size (20-200 nm) - This is the optimal size for the nanoparticle, it is very effective for wide variety of delivery.
- Encapsulation- To achieve therapeutic dosage, high percentage of agent should be used for encapsulation of nanoparticle which will protect the drug from unwanted degradation.
- Stability- The surface of the nanoparticles should be resistant to the differences in the pH values, temperature, and ionic strength.
- More Circulation Time- The nanoparticle must have reasonable circulation time in circulatory system so that it completes its task.
- Specific targeting- Targeting could be active or passive (by enhanced EPR effect). Targeting must ensures that there is least side effect to healthy tissue and desired lesion will uptake the drug in more concentration.
- Clearance of Nanoparticle-There must be clearance procedure for nanoparticle vehicle, so that the long term side effect will be avoided and there will be no interference with biological functions [44].

Nanoparticles for targeted drug delivery in breast cancer

Multidrug Resistant (MDR) has seriously hindered the treatment of breast cancer.

Nanotechnology allows to overcome the difficulties arise due to chemotherapeutic agent because it has multispecific drug transporters such as Multidrug resistant protein 1 (MRP1), P-glycoprotein and BCRP (Breast cancer resistant protein). Majorly organic and inorganic nanoparticles are used for drug delivery. Organic particles like micelles, liposomes, polymers, dendrimers and inorganic particles like Gold nanoparticles, SPIO nanoparticles and Quantum dots have been extensively used for the drug targeting.

They have unique property to target the drug at the specific tumor site by not affecting the healthy cells. Other than organic and inorganic drug delivery, localized drug delivery and Receptor based drug delivery are also practiced for the treatment of breast cancer (Yezhelyev *et al.*, 2006) [40].

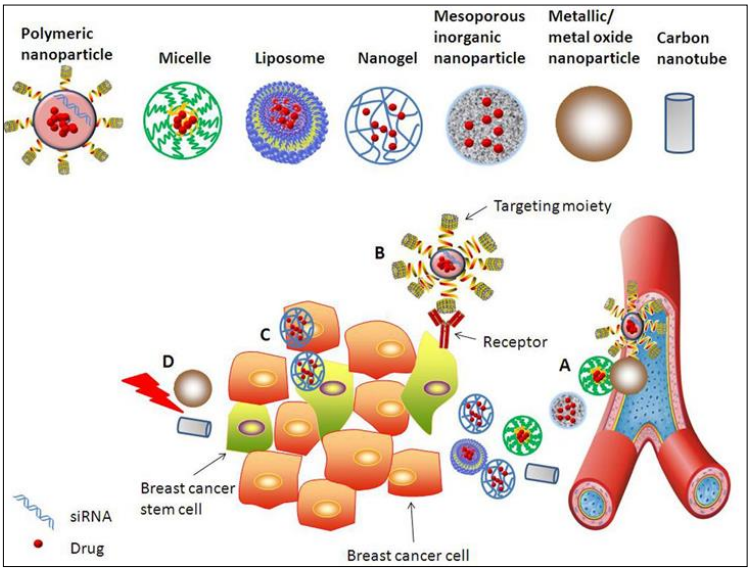

Fig 4: Various Approaches To Target Breast Cancer Cells By Using Nanocarriers (He *et al.*, 2016) [12].

Organic drug delivery approaches

Micelles

Micelles have been extensively used to hydrophobic drugs to the tumor. Micelles utilize passive targeting for the accumulation of drugs by enhancing the permeation and retention effect. In a polymeric micelle drug loading can be done by either covalent attachment or by physical encapsulation. The first polymeric micelle to be developed was paclitaxel, Genexol-PM (PEG- poly (D, L-lactide)-paclitaxel). Multi functional polyster micelles can also be effective for the treatment of breast cancer. Micelles shown to overcome P-gp efflux. Sometimes antibody is bound to the surface of micelle, which is used to treat breast adenocarcinoma. Treatment of HER-2 positive breast cancer can be performed by using HER-2 monoclonal antibody conjugated to micelle. This shows high efficacy as compare to simple treatments. Multifunctional micelles have been actively developed for the treatment of breast cancer and it will become conventional in future (Lee *et al.*, 2009) [19].

Liposomes

Liposomes as a nanocarrier were first described in 1965. Till date there are 11 approved formulations for clinical use. Liposomes are colloidal structures; they are composed of lipid bilayer (Dadwal, Baldi and Kumar Narang, 2018) [6]. Outer lipid bilayer surrounds a central aqueous layer. They have unique property to encapsulate hydrophilic agents. To improve their stability the liposomes can also be coated with polyethylene glycol. Other applications of breast cancer in delivery system include decreasing the side effects of chemotherapeutic drugs, alkaloids, platinum etc. Liposomes can improve the treatment of breast cancer by increasing the drug accumulation (Park, 2002) [26]. It has been observed that the cardiotoxic effects of anthracycline is been reduced when it is encapsulated in liposomes. The coming generations of liposomes (immune liposomes), synthesize in a way that they may deliver the drug at specific receptor site.

Polymers

Biopolymers nanoparticle based delivery provides a series of benefits. Polymeric nanoparticles have optimum size (3-200 nm). Polymers bound to copolymers have been extensively used for the drug delivery. Polymers can be synthetic, natural, biodegradable and nonbiodegradable. Gelatin, chitosan, cellulose are the natural polymers that has been widely used for the drug delivery. Synthetic polymers such as poly-(lactic-co-glycolide), polylactide have high rate of solubility and permeability. Those polymers are biocompatible; they have good drug stability and release. Drug delivery system for HER-2 positive breast cancer has been proposed by lee and wans via HER-2 targeted HPMA copolymer conjugated in combination with tyrosine kinase inhibitor. The synergistic effect of a drug conjugate delivery has been observed (Calzoni *et al.*, 2019) [4].

Dendrimers

These are the synthetic polymers having dimensions in nanometers. Dendrimers are composed of many monomers that are protruding outwards from the centre core. The negatively charged dendrimer and the neutral dendrimers are biostable whereas positively charged dendrimer may show some toxic effects. If the PEGylation of dendrimer is done, it will enhance its retention time and improves the distribution characteristics. Due to these properties the dendrimers improve the research in development of new drug carrier, which may improve the breast cancer treatment. The delivering of dendrimer based nanoparticle for transport specific drug into a particular area of malignant cells could be best approach for the treatment of breast cancer (Madaan *et al.*, 2014) [22].

Inorganic drug delivery approaches

Gold Nanoparticles

It is one of the first metals which have been discovered. Gold nanoparticles are most stable nanoparticles. It can be modified by coating its core with silica. Gold nanoparticles show high affinity towards thiols, amines, disulfide etc. Due to its strong affinity it allows different biological ligands like DNA, antibodies, peptides to coat the gold particles. Gold have capability to protect the therapeutic agent from enzymatic degradation in case of breast cancer. Gold nanoparticles show selective intracellular delivery of tamoxifen which has been target to ER (+) breast cancer.

Sometimes gold nanoparticles are conjugated with herceptin. This will increase the uptake of gold nanoparticles. Although herceptin is effective against HER-2 over expression in breast cancer. Gold nanoparticles show 99% specificity and sensitivity, they can also be used as a diagnostic marker. In a report it has been shown that the MDA-MB-231 cells of triple negative breast cancer were inhibited by galic acid capped with gold nanoparticles (Ojea-Jimenez *et al.*, 2013) [24].

SPIO Nanoparticles

Super para magnetic Iron oxides (SPIO) can be used in various fields like immunoassay, repairing of tissue and for imaging in magnetic field. SPIOs can easily modify their physical and chemical properties like shape, size and surface properties. SPIOs nanoparticles can be used to target surface markers on tumor. SPIO is basically made up of two components an iron oxide core and hydrophilic coating of magnetic particle biomolecule. This will help to target the specific tissue area. However, detailed knowledge of breast cancer treatment using SPIOs nanoparticles is still to be explored. But in future it may apply as an effective treatment agent in breast cancer (Wärnberg *et al.*, 2019) [37].

Quantum Dots (QD)

They are the crystals of size ranges between 2-10 nm. QD nanocrystals have optical properties and they are very bright. They have many applications in the biological field. QDs can be conjugated with antibodies, peptides and other particles which can be used in the treatment of breast cancer. Surface can be modified to increase the solubility and reduce the toxicity of the drug. In recent years cadmium free QD seeks more attention because of its biostability (Radenkovic *et al.*, 2016) [31].

Localized drug delivery

The development of such kind of approaches enables the drug to specifically target the tumor tissue. It decreases the side effects of the drugs and increases its solubility. Localized drug delivery shows its great effect on the early stage cancer. The synthetic as well as natural polymers are being used for the treatment of breast cancer (Wolinsky, Colson and Grinstaff, 2012) [38]. Whereas hydrogel formation, nanofibres and intraductal injection can further improves the treatment of breast cancer and can be used as an effective treatment in future.

Nanofibres

A nanofibre is characterized by its strength and its chemical properties. It is made up of cross linked polymers. For drug delivery approaches the nanofibers are synthesized using biodegradable polymers like polyethylene glycol, polyethylene oxide, PVA, PCL, chitosan etc. Another nanofibre, electrospun allow cells to grow on a fabricated tissue. It has been found that curcumin-loaded nanofibres were tested on MCF-7 breast cancer cell line, it found 15% more effective than the available commercial drugs (Jayakumar *et al.*, 2010) [14].

Hydrogels

Hydrogels can be physically and chemically linked to a polymer chain, these are water in- soluble compounds. Hydrogels can be made from the synthetic and natural polymers. Proteins and glycosaminoglycan being components of breast can be used to fabricate the hydrogels, it supports the growth of breast cells. Hydrogels are developed in the form of nanoparticles for the treatment of tumor. Chitosan hydrogels based on temperature-responsive hydroxyl butyl, poly (vinyl alcohol), poly (ethylene glycol), chitosan chloride and chitosan/bifunctional aldehyde have been investigated, but not tested in the preclinical trial for breast cancer application. An efficient delivery can be achieved if nanoparticles will embed in the hydrogels (Segovia *et al.*, 2014) [33].

Intraductal injections

If there is any kind of molecular or morphological change in the epithelial cells of the breast ducts, it increases the risk of breast cancer. Duct carries milk to the nipple; approximately 80% of women are diagnosed with Ductal carcinoma, which is a non invasive cancer in the inner lining of the ducts. Microcathetar has been extensively used to remove the ductal cells, this process shows high efficacy in collecting the breast cells. Chemotherapeutic drugs can be provided by intraductal injection to achieve localized drug delivery. 5-fluorouracil and estradiol can be given by intraductal injections in case of mammary papilloma to enhance the immune response (Yang *et al.*, 2017) [39].

Receptor-based drug delivery

Multiple receptors are responsible for the growth of the breast tumor and these receptors can be used as an avenue for the treatment of breast cancer. Studies are still going on for targeting the receptor for metastatic breast cancer. Studies have been conducted by different researchers to target receptors like HER-2, EGFR, IGF-IR and VEGFR for the treatment of breast cancer. All the receptors are responsible for carrying out different pathways in breast tumor development (Lu *et al.*, 2013) [21].

HER-2

HER-2 over expression has been seen in breast cancer patients. It is a member of EFGR family and plays a great role in generation of tumor. Anti HER-2 therapies has been given to patient, monoclonal antibody is targeted against the antigen. It has been observed that this therapy improves the survival rate of patients (15-30%) with breast cancer (Valabrega, Montemurro and Aglietta, 2007) [36]. Trastuzumab is the monoclonal antibody given to the HER-2 positive breast cancer patient. If this antibody is given in combination with other drugs like taxanes it will enhance the survival rate up to 80%. Many randomized combinations of chemotherapeutic drugs and trastuzumab are in clinical trial phase I and II which may show some improvement in the survival rate of breast cancer patients (Montemurro and Aglietta, 2005) [23].

EFGR

In triple negative breast cancer and inflammatory breast cancer the over expressions of EFGR has been observed. There are different members of EFGR family, EGFR (also known as ErbB1 and HER-1), HER-2 (also known as HER-2/neu and ErbB2), ErbB3 (HER3), and ErbB4 (HER4). EFGR over expression is directly linked to increased copy number and the protein amount in case of breast cancer. The increased copy number of gene in EFGR is observed in ER, PR and HER-2 negative breast cancers. Several drugs have

been developed to target EFGR but their clinical outcome was poor (Valabrega, Montemurro and Aglietta, 2007) [36].

IGF-IR

The growth of breast cancer is regulated by receptor tyrosine kinase (RTK), thus for the treatment of breast cancer this receptor can be targeted. Normal breast cells growth is mediated by IGF-IR, this is also responsible for apoptosis of tumor cells. RTK has two main domains intracellular and extracellular domains. According to some reports the over expression of IGF-IR at the early stage of breast cancer was observed. The negative expression of IGF-IR, using monoclonal antibodies, antisense IGF-IR, catechols, and transfection methods, can inhibit the growth of tumor in breast cancer (Youngren *et al.*, 2005) [42].

VEGF

When VEGF is up regulated by several hormones and cytokines it serves as a primary stimulus of angiogenesis. It is linked with the progression and development of metastatic breast cancer through various receptors like-VEGFR-2, VEGFR-1, VEGFR-C. It is important to target VEGFRs. Monoclonal antibody can be targeted against VEGFRs to slow the tumor growth and destroy the tumor blood vessels. The siRNA as well as anti-VEGF antibody therapy is already in clinical trials for regulation of VEGF activity (Rao and Cooley, 1995) [32].

Conclusion

Nanoparticles have so many advantages and applications. We can rely on nanoparticles as there is controlled release of drugs. Nanoparticles chemotherapeutics shows influence on breast cancer treatment. Nanoparticles due to no side effect are preferred over traditional chemotherapeutic drugs. However, there are still limited clinical data and a limited number of nanotherapeutics approved for clinical use.

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