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LIPID – BASED NANOCARRIERS FOR DELIVRING BREAST CANCER THERAPEUTIC

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ABSTRACT

Breast cancer is by far the commonest and second leading cancer in women of western country. Treatment options of breast cancer are surgery, radiation and chemotherapy. Therapeutic options for breast cancer are limited, therapeutically considerable and associated with different toxicities. The application of nanotechnology to medicine helps to defeat the limitations relating to chemotherapy which exhibited the possibility to treat or target breast cancer. Among, the nanoparticles a variety of lipid nanoparticles namely liposomes, solid lipid nanoparticles, nanostructures lipid carrier and lipid polymers hybrid nanoparticles have been developed over the years for the breast cancer therapy and data are accepted. In future, the use of nanotechnology could modernize the entire of breast cancer treatment. So, the present review highlights the lipid-based nanocarriers for breast cancer treatment.

KEYWORDS: Breast cancer, lipid, lipid polymer hybrid nanoparticles, liposomes, nanostructure lipid carriers, solid lipid nanoparticles.

INTRODUCTION

Breast cancer is the most common diseases and holds second rank in the mortality rate of women. In, 2017 it's estimated that about 30% of breast cancer are diagnosed. According to the World Health Organization (WHO), by 2050, it is expected that 27 million new breast cancer cases and 17.5 million breast cancer deaths will arise per annum.[1] Metastatic action of the breast tumors leaves the disease condition mysterious and not curable. Current therapies for breast cancer comprise radiation therapy, chemotherapy and endocrine therapy – has enriched the therapeutic effect but the toxicity and side effects related with these

therapies are obstructing the clinical efficacy.[2] Most of the cytotoxic drugs are used clinically are chemotherapeutics are administered into systemic circulation. Administering low molecular weight chemotherapeutics agents into systemic circulation which exhibit rapid clearance, low pharmacokinetics profile and sub – optimal tissue distribution and a small fraction reach the tumour/tumour cell. A hydrophobic natured chemotherapeutics agent exhibits huge volume of distribution leading to higher accumulation at healthy tissue site and causes toxicity. Chemotherapeutics agents are extremely susceptible to expand multi-drug resistance (MDR) in the tumors. Investigation and enlargement of a new technology are important to treat breast cancer, which could successfully target tumor cells without killing healthy cells.[3]

Conventional Breast Cancer Therapy

Presently, various conventional therapies like radiation therapy, chemotherapy, hormonal therapy, and immunotherapy are used for the treatment of breast cancer. Cancer cells that may not be seen during surgery can be killed by radiation to decrease the risk of local recurrence of cancer. Radiation therapy is a process in which cancer cells are exposed to high levels of radiation directly. Radiation therapy after surgery shrinks the tumor in combination with chemotherapy. But there are some side-effects of radiation therapy, such as decreased sensation in the breast tissue or under the arm, skin problems in the treated area (including soreness, itching, peeling, and/or redness) and at the end of treatment the skin may become moist and weepy.[4]

The reason of hormonal therapy is either adding or blocking hormones. The female hormones estrogen and progesterone can promote the growth of some breast cancer cells. Therefore hormone therapy is necessary to block or lower the levels of estrogen and progesterone to stop growth of cancer cells. Several types of hormonal drugs used for primary breast cancer include Tamoxifen, Toremifene, Arimidex, Zoladex, etc.[5]

In chemotherapy cytotoxic drugs are administered to kill cancer cells. Chemotherapy may be suggested as adjuvant chemotherapy or neoadjuvant chemotherapy. Adjuvant chemotherapy is the systemic therapy given to patients after surgery to treat undetected breast cancer cells. Neoadjuvant chemotherapy is given earlier than surgery to shrink large cancers so that they can easily be detached by lumpectomy. It is reported clinically that chemotherapy is most efficient when given in combinations of more than one drug. The most common side-effects are hair loss, mouth sores, loss of appetite, nausea, vomiting, increased chance of infections

(due to low white blood cell counts), easy bleeding (due to low blood platelet counts), and fatigue.[6]

Application of nanotechnology for breast cancer therapy

Nanotechnology is no longer a new concept and creating higher impact in every part of the health care system. Nanomedecine- nanotherapeutics- nanotheranostics are the terminologies coined of because of the utilization of the nanosized particles in the field of health care. Nanotechnology based approaches used to support clinical improvement from a disease also help to understand the interaction of malignant cells with their microenvironment.[7] Nanoparticles delivery has been demonstrated to promise high loading capacity, less toxicity, and stability of the drugs or biomolecules compared to traditional chemotherapeutic drugs. Nanomedicine, which may be nanoparticulated or nanocarriers are proposed to design in the range of nanometer to several hundred nm as per the condition and usage. Tremendous efforts and time have been spent to shift this technology from pre-clinical stage to commercialization stage.[7,8]

Lipid - Based nanocarriers

Among the nanocarriers, lipid-based nanocarriers have great potential to solubilize, encapsulate and deliver active molecules in a programmed pattern to attain bioavailability and avoid side-effects.[9,10] These drug carriers are made up of biocompatible lipids, such as phospholipids, cholesterol and triglycerides. Several advantages of the lipid matrix make the lipid-based nanocarriers as an idealistic drug delivery system. Bio-compatibility and bio-degradability characteristics of these systems are level to be less toxic as compared to other drug delivery systems, such as polymeric nanoparticles.[11,12] A number of recent reviews have provided perspectives on the use of various types of nanocarriers as therapeutic and diagnostic tools in cancer research.

Liposomes

Liposomes are spherical phospholipid vesicles composed of a bilayer membrane that surrounds an aqueous interior. Both lipophilic and hydrophilic drugs can be entrapped into liposomes because of their biphasic character. Lipophilic drugs are very poorly soluble in water, hence entrapped in the lipid bilayer of liposomes. Hydrophilic drugs may be entrapped within the aqueous core of liposomes or situated in the external water phase. The preparation procedure and bilayer composition of liposome affects the percentage entrapment of hydrophilic drug.[13] These colloidal carriers are made up of bio-degradable, bio-compatible,

non-immunogenic natural phospholipids, which can encapsulate water-soluble, fat soluble, amphiphilic, biphasic insoluble drugs and cytotoxic agents into their aqueous core surrounded by unilamellar/ multilamellar membranes.[14,15] Liposomes have gained the attention of conventional cancer chemotherapeutics because as a drug delivery system, they can elevate the concentration of drug at tumor sites and can decrease the drug concentration at normal tissues. Liposomes reduce the drug toxicities, such as cardiotoxicity and raise the therapeutic effect by varying the drug pharmacokinetics and bio-distribution. Lipids used for the liposomal preparation are derived from natural origin egg yolk or soya bean oil, which is safe for parenteral administration. Moreover, conventional liposomes have major limitations as they are fastly cleared by RES due to adsorption of opsonin proteins on the phospholipid membrane of liposomes. Drug-containing liposomes of diameters approximately 50–200 nm are easily escaped from the blood into the tumor interstitial space through gaps between irregular endothelial cells. Liposomal drug delivery to tumor is affected by long circulation time, stability (drug retention), and small vesicle size of liposome.[16]

Targeted liposomal drug delivery

Active targeted nanoparticles, a novel nanoscale approach has been developing for the localization and cellular internalization in the tumor sites. Growth factors, hormones, receptor expression, protein up regulations are involved in signaling pathways for tumor development and metastasis have been identified for the site-specific targeting, internalization and localization of liposomes in the tumors therapeutic, diagnostic and theranostic approaches. Active targeted nanoparticles are the surface-modified or functionalized passive targeted nanoparticles are successful in tumor targeting and site specific release of the chemotherapeutic.[17] Antibodies, peptides, nucleic acid aptamers, carbohydrates and some molecules are the ligands used to conjugate the nanoparticles for the active targeting of tumors. Important targets for the induction of apoptosis or inhibition of anti-apoptosis, angiogenesis, cell-cycle arrest and signal transduction in the breast cancer treatment. In vitro and in vivo studies which have concentrated in active targeting of breast cancer by the liposomes.[18]

Solid lipid nanoparticles

SLNs are bio-compatible; sub-micron sized colloidal drug delivery systems, which are designed by replacing the oil by solid lipid in the emulsions. They provide higher entrapment efficiency, higher loading, greater surface area, simpler scale-up and manufacture and less

toxic than the polymer, which potentiate the activity of the drug encapsulated in the lipid core.[19] SLNs exhibit sustained drug release and highly stable than the liposomes and even sterilization carried out during the manufacture of liposomes can be bypassed by the SLNs. The therapeutic utility of nanoemulsions is eclipsed by unpredictable drug release and of nanocrystals by poor solubilization of drug in biological fluids can be overcome by SLNs. Lipids present in the SLNs are highly purified triglycerides or waxes, calixarenes and sterols. Lipophilic drugs face solubility and bioavailability problems, which can be overcome by delivering through SLNs. SLNs, are capable of loading of hydrophilic/hydrophobic compounds, controlled and extended drug release, bypass the reticulo endothelial system and deliver the chemotherapeutic at the site of action. Solid lipid nanoparticles exhibit controlled and sustained drug release irrespective to various pH environments. So, delay in elimination half-life alters the systemic circulation time of the drug. Solid lipid nanoparticles encapsulate poorly soluble and hydrophobic natured drugs, which are facing bioavailability and cellular uptake limitations.[20]

Nanostructured lipid carriers

Nanostructured lipid carriers (NLCs) are the second generation of SLNs, which are a combination of different lipids, i.e. solid lipid matrix with a certain content of a liquid lipid.[21] It has a variety of features, i.e. controlled drug release, site-specific targeting and drug accumulation at site of action. This carrier system has high tolerability due to presence of physiological and bio-compatible lipids.[22] NLCs show higher drug loading capacity, lower risk of gelation and low drug leakage during storage caused by lipid polymorphism. It has prolonged exposure of tumor cells to antitumor drug, EPR effect and subsequently increases the therapeutic effect of anti-tumor drug.[21] In NLCs, addition of liquid lipid to solid lipid creates massive crystal disorder resultant imperfections in lipid matrix. This helps in the higher lodging of drug into the space thereby higher drug loading will be achieved.[23, 24]

Lipid- polymer hybrid nanoparticles

Polymeric nanoparticles exhibit good structural integrity, tissue penetrable, various methods/polymer available for preparation, stable in biological fluids/during storage, ease of functionalization for active targeting and avoid RES clearance resulting in increased circulation time. Limitations associated with polymeric nanoparticles scale-up, organic solvent usage in the

preparation and degradation; whereas, liposomes have been recognized as a superior drug delivery system due to its biocompatibility with biological components. They are tunable, bio-degradable, non-toxic, non-immunogenic, surface modifiable. Drawbacks associated with liposomes are less stable during storage, drug leakage and sterilization.[24] To mitigate the problems associated with both systems amalgamation of lipid and polymer brought novel drug delivery systems termed as lipid polymer hybrid nanoparticles LPN.[25]

CONCLUSION

The preference of appropriate nanocarriers is a complicated one. It is essential to recognize the key nanoparticles features such as properties, size, targeting ligand, and charge to get better design for oncology applications. Nanoparticles therapeutics has been used for several treatments of most cancers. Though the field of nanomedecine is rising rapidly, there are still an incomplete number of nanocarriers approved by the FDA and limited existing clinical data. More clinical trials are essential for better understanding and the advantages and disadvantages of nanoparticles therapeutics. Well-designed studies are significant for development of these drugs. Lab-scale to large-scale approach is strongly recommended to bring nanomedicine for the clinical utility. Advance research is desirable to develop new nanotherapeutics incorporating a range of characteristics along with high-quality experimental design in order to attain improvements in treatments and nanoparticles targeting to overcome current limitations.

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