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Liposomes as targeted drug delivery systems in the treatment of breast cancer.

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Abstract *:* Solid tumors such as breast cancer have historically provided many challenges to anti-cancer therapy. Therapeutic hurdles to drug penetration in solid tumors include heterogeneous vascular supply and high interstitial pressures within tumor tissue, particularly in necrotic zones, lower pH and presence of leaky vasculature leading to reduced therapeutic response. Liposome based drug delivery systems offer the potential to enhance the therapeutic index of anti-cancer agents, either by increasing the drug concentration in tumor cells and by decreasing the exposure in normal tissues exploiting enhanced permeability and retention effect phenomenon and by utilizing targeting strategies. This review discusses recent trends in liposome-based drug delivery system both for diagnosis and treatment of breast cancer.

Index Terms - Liposomes, drug delivery systems, cancer therapy.

Introduction:

Drug delivery systems offer the potential to enhance the therapeutic index of anticancer agents, either by increasing the drug concentration in tumor cells or by decreasing the exposure in normal host tissues. This commentary will discuss some of the recent trends in liposome-based drug delivery systems for breast cancer therapy. Liposomes, the most widely studied nano-drug carriers in drug delivery, are sphere-shaped vesicles consisting of one or more phospholipid bilayers. Compared with traditional drug delivery systems, liposomes exhibit prominent properties that include targeted delivery, high biocompatibility, biodegradability, easy functionalization, low toxicity, improvements in the sustained release of the drug it carries and improved therapeutic indices. In the wake of the rapid development of nanotechnology, the studies of liposome composition have become increasingly extensive. The molecular diversity of liposome composition. which includes long-circulating PEGylated liposomes, ligand-functionalized liposomes, stimuli-responsive liposomes, and advanced cell membrane-coated biomimetic nanocarriers, endows their drug delivery with unique physiological functions. Solid tumors such as breast cancer have historically provided many challenges to systemic therapy. Theoretical barriers to drug penetration in solid tumors include heterogeneous vascular supply and high interstitial pressures within tumor tissue, particularly in necrotic zones. Delivery systems can even exacerbate these problems due to the slow diffusion of macromolecular agents through tumor tissue. However, delivery systems have been developed to exploit a feature of tumor microphysiology often referred to as the 'enhanced permeability and retention' effect. This effect is a consequence of the dysregulated nature of tumor angiogenesis, which characteristically involves structural and physiologic defects leading to hyperpermeability. Macromolecular agents with highly restricted volumes of distribution and the capacity for greatly prolonged circulation will preferentially extravasate from these abnormal vessels and accumulate in tumor tissue. Thel leading examples of such passively targeted agents include long circulating liposomal drugs.

Breast cancer involving the chest wall:

A special problem in the management of advanced breast cancer is that of chest wall recurrence/metastasis, which is typically highly morbid and difficult to treat. Photodynamic therapy, in which systemically administered photosensitive compounds are activated by an external light source, can be considered a related strategy to drug delivery and is under investigation for the treatment of superficial breast tumors. In a multimodality strategy, hyperthermia (which is currently used to enhance the efficacy of external beam radiation for chest wall metastasis) has been used to modulate delivery of liposomal drugs. In animal models the application of hyperthermia to subcutaneous tumors concomitant with or prior to intravenous administration of long circulating liposomes results in a marked increase in liposome accumulation within tumor tissue. The mechanism for this hyperthermia-enhanced liposome delivery appears to be via heat-induced changes in vascular permeability and microcirculatory dynamics, which further facilitate liposome extravasation from tumor vessels In a phase I/II clinical trial of metastatic breast cancer involving the chest wall, sequential hyperthermia followed by pegylated liposomal doxorubicin (Doxil") was very well tolerated and produced objective responses in the majority of chest wall tumors. It was notable that all patients had extensive prior treatment, and most had recurred or progressed after radiation and multiple chemotherapy regimens Hyperthermia can also be used in conjunction with ther mosensitive liposomes, which are being developed for heat-triggered release of encapsulated drug in tumor tissue.

Liposomes for Cancer Therapy:

Compared with traditional drug delivery systems, liposomes exhibit better biological properties, including high biocompatibility, low toxicity, easy surface modification, high targeting, encapsulation of various drugs, and protection from degradation. Given these merits, several liposomal drug products have been successfully approved and used in clinics over recent decades. Among these, Doxil (Doxorubicin HCI liposome injection) was the first liposomal product approved by the FDA in 1995. In fact, the progress of nanoliposomes has promoted the treatment of cancer.

Clinically used liposomes and their uses.

Clinical Products	Active Agent	Indication
Doxil®	Doxorubicin	Ovarian, breast cancer, Kaposi's sarcoma
DaunoXome®	Daunorubicin	AIDS-related Kaposi's sarcoma
Mepact®	Mifamurtide	High-grade, resectable, non-metastatic osteosarcoma
Marqibo®	Vincristine	Acute lymphoblastic leukaemia
Vyxeos®	Daunorubicin and Cytarabine	Adults with high-risk acute myeloid leukemia
Depocyt®	Cytarabine/Ara-C	Neoplastic meningitis
Lipusu®	Paclitaxel	Gastric carcinoma

ThermoDox, a liposomal drug carrier with lyso-thermosensitive liposomal DOX, is the first heat-activated formulation to be used in human clinical studies. When the temperature rises to 40-45 C, the thermosensitive liposomes rapidly change their structure to release DOX into the targeted site. In clinical trials, ThermoDox has been combined with radiofrequency ablation to treat hepatocellular carcinoma. However, the OPTIMA trial did not achieve the endpoints, though this did not mean that ThermoDox was not feasible. Early clinical data of ThermoDox has demonstrated feasibility, safety and activity. Currently, in a new phase 1 trial, the University of Oxford explored the safety and feasibility of combining ThermoDox with focused ultrasound for the treatment of non-resectable pancreatic cancer. Josanne S et al first explored the phase I feasibility study of a combination of ThermoDox cyclophosphamide, and magnetic resonance guided high-intensity focused ultrasound-induced hyperthermia in patients with stage IV breast cancer.

Myoceto, a non-PEGylated liposomal DOX, is combined with cyclophosphamide for first-line treatment of patients with metastatic breast cancer. Compared with free DOX and cyclophosphamide, Myoceto reduces cardiotoxicity and retains its antitumor efficacy. EndoTAG-ITM, a paclitaxel-loaded cationic liposome formulation, has been approved by the FDA. Cationic liposomes have been shown to target angiogenesis endothelial cells specifically, therefore, EndoTAG-1 TM can inhibit tumor growth and metastasis by reducing tumor blood supply. Sebastian et al. demonstrated, in a phase VTI trial of EndoTAG-1, that infusion of 32 mg total lipid/kg body weight

EndoTAG-1 was safe and had an antiangiogenic effect in human head and neck squamous cell carcinoma.

Cisplatin is a highly cytotoxic drug that inhibits DNA synthesis in tumor cells by creating inter-and intrachain cross-links, Therefore, cisplatin is still the first-line chemotherapy drug for various cancer types. However, cisplatin has serious side effects including nephrotoxicity, nausea and vomiting, ototoxicity, and allergic responses. To reduce the systemic toxicity of cisplatin, cisplatin liposomal preparations have been developed. Lipo Platinum is an FDA-approved cytotoxic agent that prolongs the circulating half-life of drugs, increases cell permeability, and accumulates drugs in tumor tissue. Yang et al. encapsulated the first-generation platinum anticancer agent cisplatin and phenethyl isothiocyanate liposomes to treat non-small cell lung carcinomas. The liposomal preparation enhanced the toxicity of this doublet to NCL-H596 non-small cell lung carcinomas cells.

Onivyde, an IRI liposome injection, was approved by the FDA in 2015 for the second-line treatment of pancreatic ductal adenocarcinoma. It is a long-circulating liposomal topoisomerase inhibitor that blocks DNA replication in cancer cells. OnivydeTM can increase the accumulation of IRI at the tumor site through the EPR effect. In human colon (HT29) and breast (BT474) cancer xenograft models, compared with free IRI, the liposomal IRI has an increased drug loading and prolonged drug half-life, resulting in a significant increase in cytotoxic activity, Onivyde, in combination with leucovorin and fluorouracil, is intended for the treatment of patients with metastatic adenocarcinoma of the pancreas who have progressed following gemcitabine-based therapy. On 9 November 2022, French pharmaceutical company Ipsen announced that the Phase Ill clinical trial of Onivyde M plus 5-fluorouracil/calcium leucovorin and oxaliplatin, as the first-line treatment for metastatic pancreatic ductal adenocarcinoma, had reached the primary endpoint.

In addition to clinical liposomal preparations, many novel liposomal drug delivery systems for cancer therapy are being developed in the laboratory. Platinum nanoparticles (nano-Pt) are highly cytotoxic and kill cancer cells by leaching Pt ions under low pH conditions [13Z]: Meanwhile, nano-Pt is also a catalase-like nanozyme. Therefore, it can be used as an oxygen-replenishing nanomaterial to solve the problem of hypoxia limitation in photodynamic therapy. Liu et al. prepared biomimetic liposome nanoplatinum by encapsulating nano-Pt and the photosensitizer vetprofen in macrophage membrane-coated liposomes. This liposome delivery system achieved deeper tumor tissue penetration while enhancing chemotherapy effectiveness with nano-Pt catalyzed oxygen delivery. Coupling MTI-MMP-activated cilengitide (MC) to DOX-loaded thermosensitive liposomes produces a novel smart nanovesicle MC-T-DOX, which can improve tumor blood perfusion,vdrug delivery, and treatment of pancreatic cancer by selectively stimulating

tumor angiogenesis. Shen et al. proposed a PEGylated liposome loaded with mannose and levamisole hydrochloride to inhibit tumor growth. This suppresses tumor growth by restraining glycolysis and mitochondrial energy metabolism in cancer cells and macrophages. In addition, liposomes, used with radiotherapy, not only enhance the therapeutic effect of local tumors, but also increase the immune response to inhibit metastatic lesions.Xing et al. developed a liposome-based, light-triggered efficient sequential delivery method for multimodal chemotherapy, antiangiogenic and anti-myeloid-derivec suppressor cell therapy in melanoma. This delivery strategy demonstrates the " effectiveness of cancer multimodal therapy targeting multiple targets at different spatial locations in the TME.

Liposomal delivery of other drugs:

The most active drugs against breast cancer are currently the anthracyclines and taxanes (paclitaxel and docetaxel), Strategies for the delivery of taxanes are under active investigation to increase tumor exposure and/or to reduce adverse effects such as neurotoxicity, edema, asthenia, and alopecia. In addition, special issues with the taxanes provide further rationale for application of delivery systems. Both paclitaxel and docetaxel are poorly soluble in aqueous solutions, and have consequently been formulated with vehicles Cremophor EL and polysorbate 80 (TWEEN), respectively. These formulations are highly allergenic, require extensive premedication, and are responsible for most of the acute toxicities observed with taxane therapy, rather than the taxanes themselves. Delivery strategies in clinical trials include liposome-encapsulated paclitaxel and poly(L-glutamic acid)-paclitaxel, a polymer conjugate. Other applications for delivery systems

in breast cancer include approved chemotherapy drugs such as vinca alkaloids, platinums, and camptothecins. In each case, it is possible that delivery systems such as liposomes on polymers could improve pharmacokinetics, could increase tumor accumulation, and/or could reduce limiting toxicities. While delivery systems for standard anticancer compounds may increase their clinical utility, there is also intense interest in developing delivery strategies for novel anticancer agents that cannot be used by themselves as drugs. Delivery systems can potentially overcome many common pharmacologic problems such as those involving solubility, in vivo stability, pharmacokinetics, tumor uptake, and toxicity. The increasing repertoire of sophisticated delivery systems may thus allow new classes of potent anticancer agents to reach clinical application. This includes not only drug delivery, but also liposome-derived systems or nucleic acid-based agents, such as antisense oligonucleotides and gene therapy constructs.

Targeted nano-liposomes for breast cancer treatment:

Actively-targeted liposomal drug delivery systems are a hugely promising concept, as it provides the advantage of specifically targeting cancer cells. This accurate targeting has many benefits, including;
(i) selective cancer cell internalization and release of the therapeutic drug which results in less side effects in healthy tissues and mitigates the risk of MDR,
(ii) the ability to across blood-brain barrier (BBB), and
(iii) the ability to identify, image, and treat metastatic, relapsed and/or breast-cancer associated cells. Both preclinical and clinical studies have demonstrated interest in using targeted nanomedicines as solid-tumor treatment.
However, although the concept of developing targeted cancer therapy seems straightforward, in practice active targeting is exceedingly challenging. In addition to requiring the presence of viable targets, liposomes must be grafted with specific targeting moieties for optimum affinity without obscuring the needed stealth aspects. Commonly, the surface of liposomes is chemically modified with various reactive groups to functionalize it (i.e., covalently or noncovalently) with a large variety of targeting agents. Six main chemical functionalization strategies are generally used, including, (a) imines-crosslinked using glutaraldehyde,
(b and c) amide-crosslinked from primary amine and free or p-nitrophenyl carbonyl-activated carboxylic acid, respectively,
(d) disulfide-crosslinked using thiol and pyridyldithiol groups,
(e) thiol-maleimide click chemistry reactions, and
(f) hydrazone-crosslinked from aldehyde and hydrazine groups.

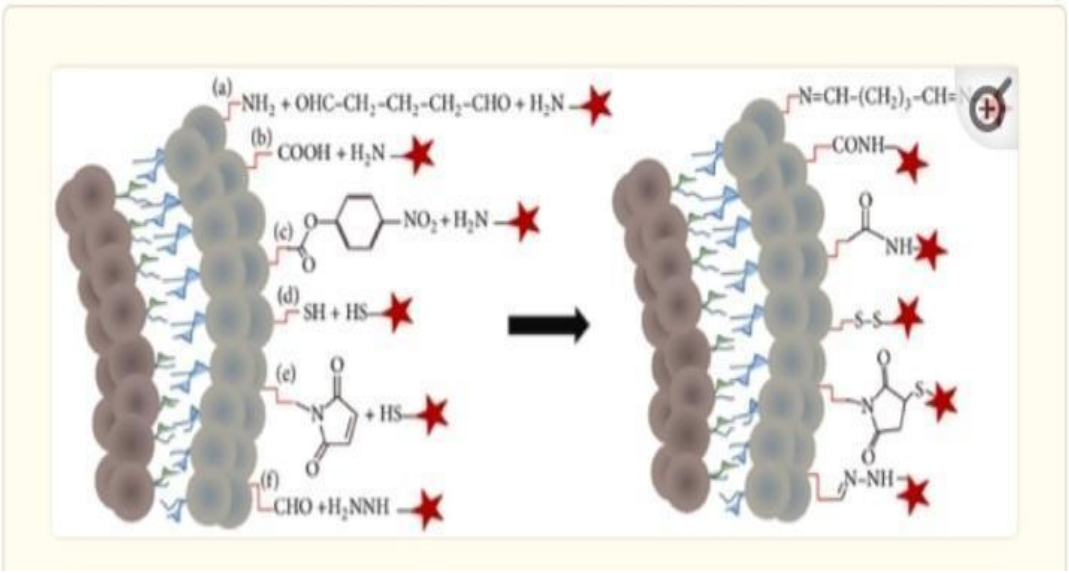
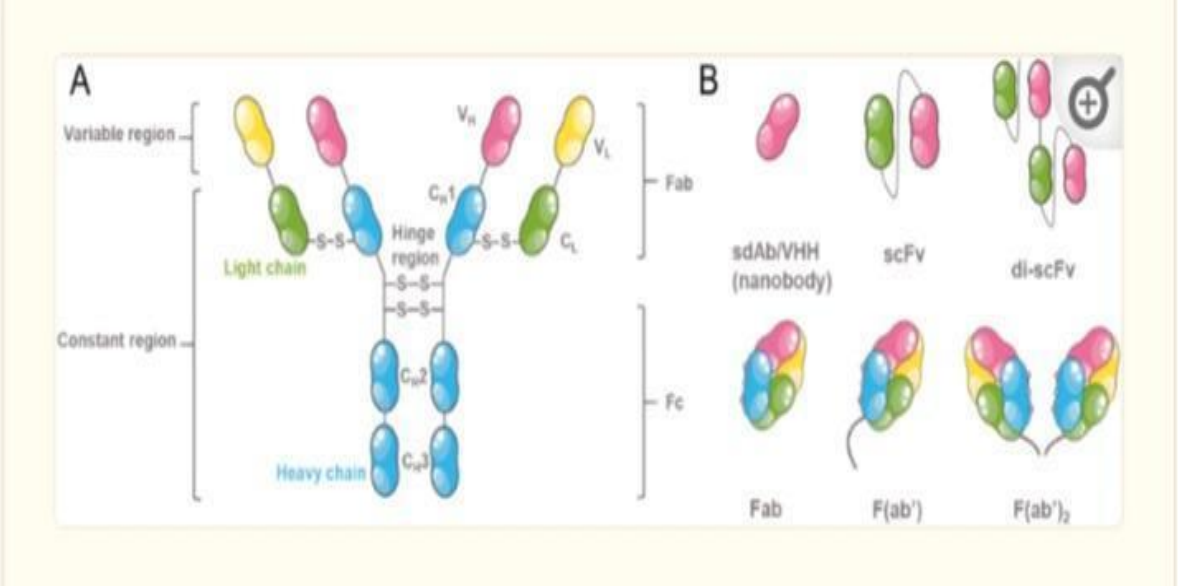


Fig: Six main chemical strategies (**a – f**) for liposomal surface functionalization. Stars represent targeting ligands.

Of these, the thiol-maleimide click chemistry reaction is one of the most popular methods with extensive literature available showing the conjugation (with or without anchored PEG) between nanoparticles and antibodies, antibody fragments, peptides, aptamers, vitamins, etc. Alternative methods for liposomal surface functionalization include adsorption or interpolation via electrostatic or hydrophobic interactions.

Targeting ligands, such as small molecules, mAbs, peptides, or aptamers, which can either directly bind to a target on or within the breast cancer or breast cancer-associated cell (e.g., a cell surface receptor or intracellular enzyme comparatively unique and abundant to the targeted cell) or be targeted to the nearby area of the tumor (e.g., acidic pH associated with the TME). Early drug-targeting studies focused on the use of whole mAbs, which are generally large, Y-shaped IgG antibodies consisting of two identical subunits of heavy and light protein chains joined by disulfide bonds. Although the whole mAbs possessed high affinity and specificity for their targets, they were also plagued with issues of poor permeability (due to their large size), immunogenicity, and high cost. Thus, it is now recognized that antibody fragments (e.gFragment antigen-binding (Fab) units and single-chain variable fragments (scFv) possess reduced immunogenicity and improved pharmacokinetic profiles. Fab fragments consist of the variable and constant regions of the heavy and light protein chains which include the paratope region, i.e., the region that recognizes and binds to targets, but lacks the tail region of the antibody, i.e., the fragment crystallizable region (Fc region).



Fab fragments can also be modified for easier immobilization with the addition of a thiol group and are then referred to as Fab' fragments. Antibody Fv fragments, such as scFv fragments, are even smaller units as they consist of only the variable paratope region of the antibody. Another popular targeting ligand moieties are peptides due to their relatively simple and low cost preparation methods, and their powerful capacity to avoid non-specific binding, and opsonization. It should be noted, however, that peptides are prone to proteolysis. Small molecules, such as sorafenib, have good permeability, and are easy and cheap to manufacture and synthesize but suffer from a lack of specificity. Lastly, aptamers are single-stranded DNA, RNA, or peptide sequences with incredible affinity and specificity towards targeted small molecules, proteins, viruses, or cells. Compared to antibodies, aptamers are smaller, more stable, and are easier to manufacture and modify with markedly improved antigen recognition and specificity but are rapidly cleared and degraded.

Conclusions:

Understanding the exact mechanism by which liposomes reach tumor sites and release loaded drugs is critical to resolving existing cancer therapy problems. Today, several liposome delivery technologies targeted for tumor targeting are being tested in clinical trials. With in-depth study, functionalized liposomes have evolved from simple vesicle structures to stimuli-responsive and cell membrane-coated liposomes. We can produce multifunctional nanocarriers by coupling numerous types of ligands on a single carrier using various surface modification methods of nanomaterials. In tumor treatment, multifunctional liposomes with prolonged release, targeted distribution, triggered release, and synergistic actions employing diverse surface functionalization and modification approaches will be essential.

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