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Review Article

VARIOUS APPROACHES OF TARGETED DELIVERY FOR CANCER TREATMENT-A REVIEW

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Abstract: Cancer drug delivery is no longer simply wrapping the drug in new formulations for different routes of delivery. Knowledge and experience from other technologies such as Nanotechnology, Brachytherapy, and Electro chemotherapy, are being brought together in developing novel methods of drug delivery. Advances in our knowledge of molecular biology of cancer and pathways involved in malignant transformation of cells are revolutionizing the approach to cancer treatment with a focus on targeted cancer therapy. The newer approaches to cancer treatment not only supplement the conventional chemotherapy and radiotherapy but also aim to prevent damage to the normal tissues and overcome drug resistance. Innovative methods of cancer treatment require new concepts of drug delivery in cancer. In this article, we review some developments in the delivery of drugs for cancer treatment and discuss some approaches in the targeted drug delivery of cancer.

Key words: Cancer, Brachytherapy, Electro chemotherapy, Nanotechnology

INTRODUCTION

Cancer illustrates two characteristics; one is uncontrolled cell growth and the second is the ability to invade and metastasize. Current cancer therapies include chemotherapy, immunotherapy and radiotherapy. Systemic chemotherapy is widely used for the treatment of cancer, but it results in only curative therapy for breast tumours. In addition, chronic administration of anticancer drugs is associated with severe systemic toxicity. Therefore, novel formulations have been developed and evaluated to improve therapy and reduce toxicity by delivering drugs directly to the target site.[2]These delivery systems include liposomes, microspheres, polymeric micelles, monoclonal antibodies, niosomes and nanoparticles, among others. The current focus in development of cancer therapies is on targeted drug delivery to provide therapeutic concentrations of anticancer agents at the site of action and spare the normal tissues. There is a vast range of strategies available for drug delivery in cancer.

DIFFERENT DRUG DELIVERY STRATEGIES

Liposomes:

Liposomes are used for site-specific drug delivery by attaching specialized molecules, such as antibodies or ligands that target specific receptors present on cancer cells. Antibody-coupled liposomes i.e., immunoliposomes that are developed from sterically stabilized liposomes have both longer circulation half-lives and targeting properties. Moreover, liposomes sustained release of the drug by acting as a reservoir for the loaded drug, thus protecting the healthy cells against the side effects of antineoplastic agents. Liposomes have been investigated widely for targeting without losing their properties and, thus, are widely accepted for breast cancer targeting for antineoplastic agents.[2] Long circulating macromolecular carriers such as liposomes can exploit the enhanced permeability and retention effect for preferential extravasation from tumor vessels. Liposomal anthracyclines have achieved highly efficient drug encapsulation, resulting in significant anticancer activity with reduced cardiotoxicity, and include versions with greatly prolonged circulation such as liposomal daunorubicin. Additional liposome constructs are being developed for the delivery of other drugs. The next generation of delivery systems will include true molecular targeting; immunoliposomes and other ligand-directed constructs represent an integration of biological components capable of tumor recognition with delivery technologies. After extravasation into tumor tissue, liposomes remain within tumor stroma as a drug-loaded depot. Liposomes eventually become subject to enzymatic degradation and/or phagocytic attack, leading to release of drug for subsequent diffusion to tumor cells. Immunoliposomes, in which mAb fragments are conjugated to liposomes, represent a new strategy for molecularly targeted drug delivery for breast cancer treatment.[4]

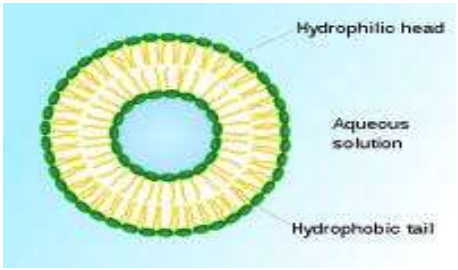

Fig.1: Liposomal Structure

Pegylation:

PEGylation, is a process of attaching the strands of the polymer PEG to molecules most typically peptides, proteins, and antibody fragments, that can help to meet the challenges of improving the safety and efficiency of many therapeutics.[5] Although the main thrust of development of pegylated liposome-encapsulated therapeutic agents has focused on systemic administration, the ability to range of agents stably in pegylated liposomes and the relative lack of direct toxicity after accidental local administration suggests that they may also have potential applications in the sphere of loco regional drug-targeting strategies. Vail et al. studied the encapsulation of doxorubicin in polyethylene glycol-coated liposomes Doxil/Caelyx [PLD], was developed to enhance the safety and efficacy of conventional doxorubicin. The liposomes alter pharmacologic and pharmacokinetic parameters of conventional doxorubicin so that drug delivery to the tumor is enhanced while toxicity normally associated with conventional doxorubicin is decreased.[6]

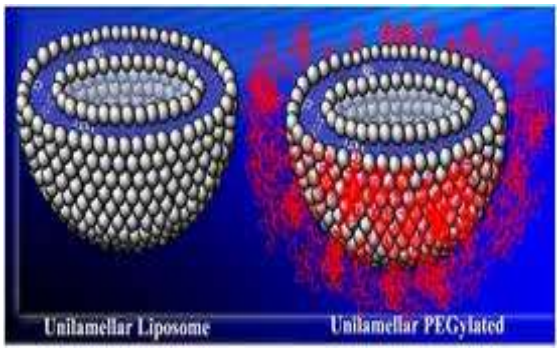

Fig.2: Pegylated liposomes

Niosomes:

Nonionic surfactant vesicles niosomes are promising drug carriers for anticancer drugs. [9] Niosomes are multilamellar vesicles formed from nonionic surfactants of the alkyl or dialkyl polyglycerol ether class and cholesterol. Adriamycin has been trapped within vesicles prepared from a monoalkyl triglycerol ether and its activity compared with adriamycin solution in human lung tumour cells grown in monolayer and spheroid culture and in tumour xenografted nude mice.[11] The pharmacokinetics of adriamycin are altered in vivo in human lung tumour-bearing nude mice, when it is administered in niosomal form. There is prolonged release of drug from the plasma compartment with significantly lower peak levels; lower peak cardiac adriamycin concentrations with a shorter tissue half-life.[11]

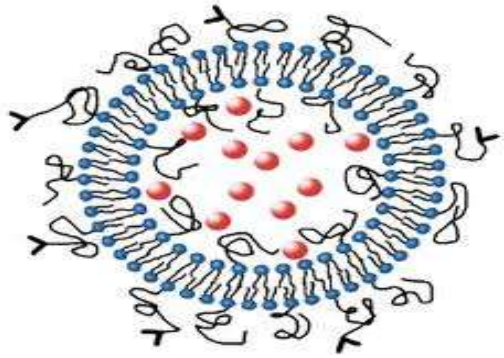

Fig.3: Stealth liposomes

Niosome encapsulated vincristine sulfate prepared by transmembrane pH gradient drug uptake process remote loading method was evaluated for toxicity and antitumour activity after administration to tumour bearing mice. The toxicity of vincristine sulfate was reduced after niosome encapsulation and anticancer activity improved, which may be due to better delivery of vincristine at the tumour site.[9]Doxorubicin, the anthracyclic antibiotic with broad spectrum anti tumor activity, shows a dose dependant irreversible cardio toxic effect. Niosomal delivery of this drug to mice bearing S-180 tumor increased their life span and decreased the rate of proliferation of sarcoma Niosomal entrapment increased the half-life of the drug, prolonged its circulation and altered its metabolism. Intravenous administration of methotrexate entrapped in niosomes to S-180 tumor bearing mice resulted in total regression of tumor and also higher plasma level and slower elimination. [10]

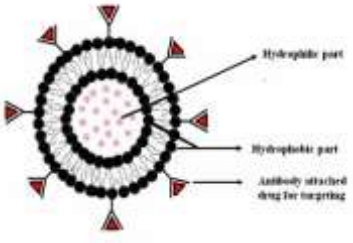

Fig.4: Structure of Niosome

Monoclonal Antibodies:

Monoclonal antibodies are a new class of agents targeted at specific receptors on cancer cells. In addition to having direct cellular effects, antibodies can carry substances, such as radioactive isotopes, toxins, and antineoplastic agents, to the targeted cells. Five monoclonal antibodies--rituximab, trastuzumab, gemtuzumab ozogamicin, alemtuzumab, and ibritumomab tiuxetan--are available for clinical use. Rituximab is active against indolent lymphomas, providing a valuable alternative for patients with relapsed or refractory disease. Trastuzumab has significant activity against HER-2-positive breast cancer, especially in combination with paclitaxel or an anthracycline and cyclophosphamide. Gemtuzumab ozogamicin is an active second-line therapy in older patients with acute myelogenous leukemia, but its role in combination regimens is unclear. The most common adverse effects of monoclonal antibodies are myelosuppression, infusion-related reactions, and hypersensitivity reactions. Investigational monoclonal antibodies include edrecolomab and tositumomab. Monoclonal antibodies have a significant role in the management of patients with advanced refractory or relapsed lymphomas and leukemias.[7]Potential uses of monoclonal antibodies in anti-cancer treatment include passive serotherapy, radioisotope conjugates, toxin-linked conjugates, and chemotherapy-monoclonal antibody conjugates. The bases for these applications have been founded in research with heterologous antisera, and in some cases with monoclonal antibodies in animal tumor models. Human trials with passive serotherapy have already begun in both hematopoietic and solid tumor malignancies. Promising results have been reported in cutaneous T cell lymphoma with anti-T cell monoclonal antibody, and in nodular lymphoma with anti-idiotype monoclonal antibody.[8]

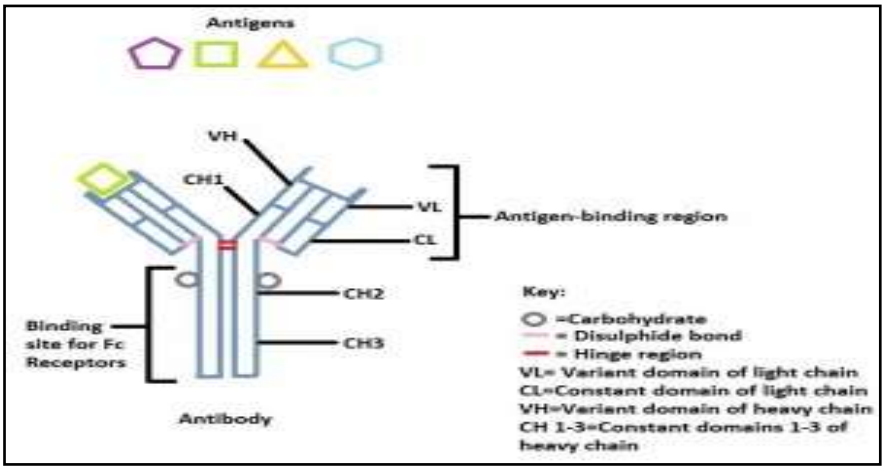

Fig.5: Structure of Monoclonal antobody

Microspheres:

Lipid microspheres can act as a carrier for antitumor agents. l,3-bis2-chloroethyl-1-nitrosourea BCNU is incorporated into microspheres by homogenizing a soybean oil solution of BCNU with egg yolk lecithin. Lipid microsphere-encapsulated BCNU showed a significantly enhanced antitumor activity with reduced toxicity in mice with L1210 leukemia when compared to the corresponding dose of free BCNU.[12] Ferrimagnetic microspheres 20–30 μm in diameter are useful as thermoseeds for inducing hyperthermia in cancers, especially for tumors located deep inside the body. The microspheres are entrapped in the capillary bed of the tumors when they are implanted through blood vessels and heat cancers locally by their hysteresis loss when placed under an alternating magnetic field.[13]TheraSphere consists of yttrium-90 a pure beta emitter microspheres, are injected into the hepatic arteries for the treatment of hepatocellular carcinoma.[14]

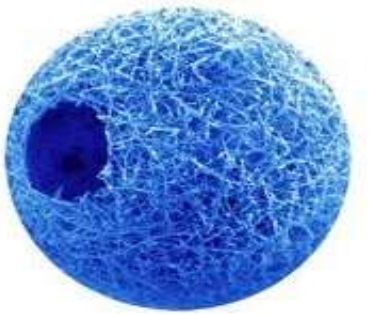

Fig.6:Structure of biodegradable nanosized microsphere.

Brachy Therapy:

Brachytherapy from the Greek word βραχυς brachys, meaning "short-distance", also known as internal radiotherapy, sealed source radiotherapy, curietherapy or endocurietherapy, is a form of radiotherapy where a radiation source is placed inside or next to the area requiring treatment. Brachytherapy is commonly used as an effective treatment for cervical, prostate, breast, and skin cancer and can also be used to treat tumours in many other body sites. Brachytherapy can be used alone or in combination with other therapies such as surgery, External Beam Radiotherapy EBRT and chemotherapy. The first suggestion to treat cancer by direct implantation of radioactive sources was apparently made by Alexander Graham Bell soon after the turn of the century.[15]

Different types of brachytherapy can be defined according to

1 The placement of the radiation sources in the target treatment area,

2 The rate or intensity of the irradiation dose delivered to the tumour,

3 The duration of dose delivery.

Source placement:

The two main types of brachytherapy treatment in terms of the placement of the radioactive source are interstitial and contact.

- In the case of interstitial brachytherapy, the sources are placed directly in the target tissue of the affected site, such as the prostate or breast.
- Contact brachytherapy involves placement of the radiation source in a space next to the target tissue. This space may be a body cavity intracavitary brachytherapy such as the cervix, uterus or vagina; a body lumen intraluminal brachytherapy such as the trachea or oesophagus; or externally surface brachytherapy such as the skin.A radiation source can also be placed in blood vessels intravascular brachytherapy for the treatment of coronary in-stent restenosis.

Duration of dose delivery:

The placement of radiation sources in the target area can be temporary or permanent.

- Temporary brachytherapy involves placement of radiation sources for a set duration usually a number of minutes or hours before being withdrawn. The specific treatment duration will depend on many different factors, including the required rate of dose delivery and the type, size and location of the cancer. In LDR and PDR brachytherapy, the source typically stays in place up to 24 hours before being removed, while in HDR brachytherapy this time is typically a few minutes.
- Permanent brachytherapy, also known as seed implantation, involves placing small LDR radioactive seeds or pellets about the size of a grain of rice in the tumour or treatment site and leaving them there permanently to gradually decay. Over a period of weeks or months, the level of radiation emitted by the sources will decline to almost zero. The inactive seeds then remain in the treatment site with no lasting effect.Permanent brachytherapy is most commonly used in the treatment of prostate cancer.

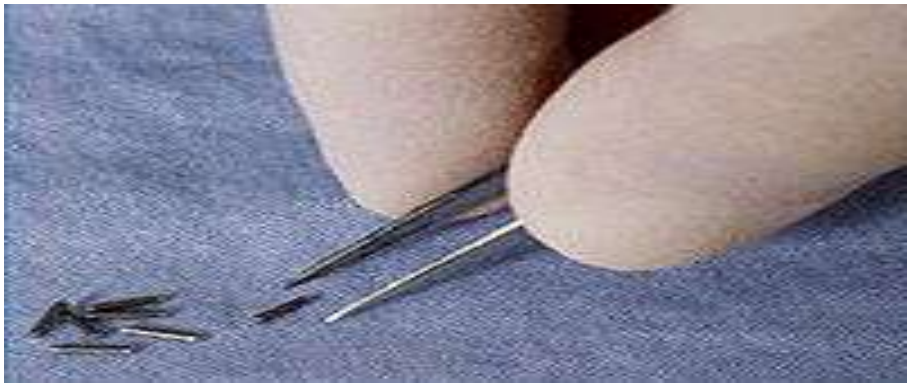

Fig.7: Permanent brachytherapy is often performed for prostate cancer using "seeds" - small radioactive rods implanted directly into the tumour

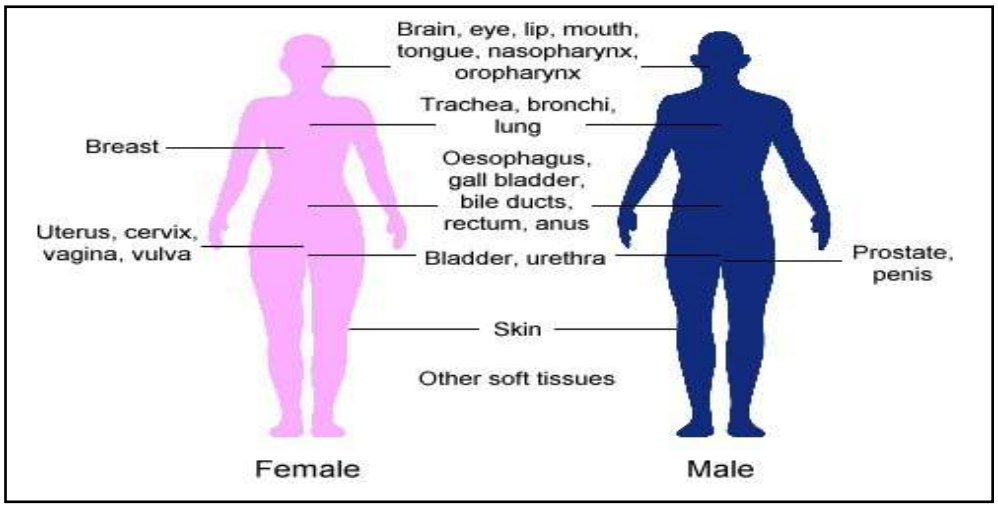

Fig.8: Body sites in which brachytherapy can be used to treat cancer

Electrochemo Therapy:

Electrochemotherapy is a therapeutic approach providing delivery into cell interior of non-permeant drugs with intracellular targets. It is based on the local application of short and intense electric pulses that transiently permeabilize cell membrane, thus allowing transport of molecules otherwise not permitted by a cellular membrane.

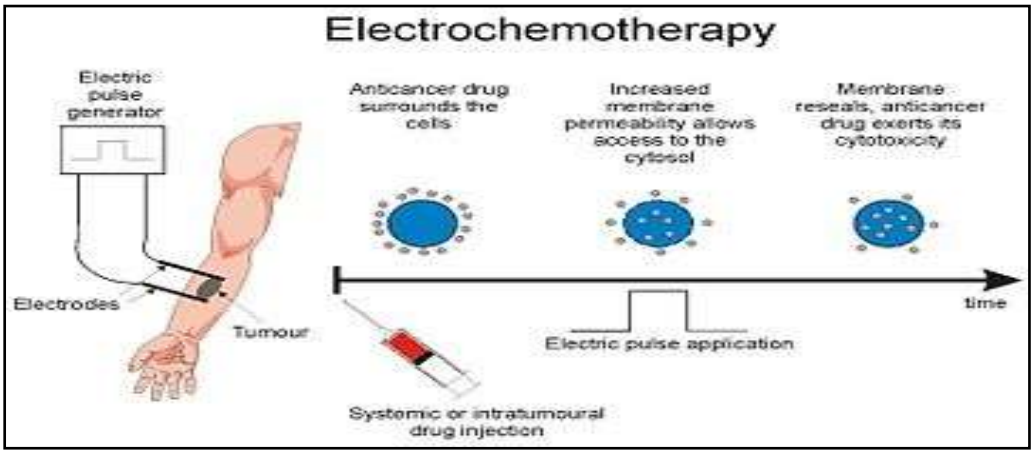

Fig.9: Electro-chemo Therapy

Electrochemotherapy is a local treatment that uses electroporation of the tumors to increase uptake of cytotoxic drugs, such as bleomycin or cisplatin. The electrochemo therapeutic treatment consists of delivering, either systemically or locally, non-permeant cytotoxic drugs e.g. bleomycin or low-permeant drugs i.e. cisplatin and applying electric pulses to the area to be treated when the concentration of the drug in the tumour is at its peak . With the delivery of the electric pulses, cells are subjected to the electric field that causes the formation of nanoscale defects on the cell membrane which alter the permeability of the membrane. At this stage and for some time after pulses are delivered, molecules of the cytotoxic agents can freely diffuse into the cytoplasm and exert their cytotoxic effect. Electrochemotherapy is now in development for treatment of deep-seated tumors, like in bones and internal organs, such as liver. The technology is available with a newly developed electric pulse generator and long needle electrodes; however the procedures for the treatment are not standardized yet. [16]

Nanotechnology:

Nanomaterials are at the cutting edge of the rapidly developing area of nanotechnology. The potential for nanoparticles in cancer drug delivery is infinite with novel new applications constantly being explored. Multifunctional nanoparticles play very significant role in cancer. Cantilevers, Nanoshells, Nanotubes, Quantum dots are some of

the nanomaterials used in the drug delivery of cancer.[3] The diagnosis and treatment of cancer have been greatly improved with the recent developments in nanotechnology. One of the promising nanoscale tools for cancer diagnosis is fluorescent nanoparticles NPs, such as organic dye-doped NPs, quantum dots that enable highly sensitive optical imaging of cancer at cellular and animal level. Furthermore, the emerging development of novel multi-functional NPs, which can be conjugated with several functional molecules simultaneously including targeting moieties, therapeutic agents and imaging probes, provides new potentials for clinical therapies and diagnostics and undoubtedly will play a critical role in cancer therapy. [18]

Table.No-1: Nanoparticles in Cancer treatment.

Nanoparticle	Size	Toxicity	Status	Application
Liposome	100-200nm	Low	Clinical use	Delivery
Small polymer	~200kDa	Low	Research	Delivery
Dendrimer	2-6nm depending on generation number	Variable depending on cell type	Phase I	Delivery
Virus	30-100nm	High	Phase II	Delivery
Hybrid System				
QD – Virus	Variable	-	Research	Imaging delivery
Metal core dendrimers	2-4nm for gold	-	Research	Delivery
Nanoshells	60-400nm	Non-toxic	Research	Imaging, treatment
Quantum Dots	2-10nm	Toxic	Commercial	Sensing, Imaging
Carbon nantoubes		Expected to be non-toxic	Research	Delivery, sensing
Single-walled	1-2nm diameter, variable length			
Multi-walled	20-25nm diameter, variable length			
Nanowires	Variable length/diameter	NA	Research	Sensing

Miscellaneous Biological Therapies:

Antisense therapy
Cell therapy
Gene therapy
Genetically modified bacteria
Oncolytic viruses
RNA interference.

CONCLUSION:

Nanotechnology is definitely a medical boon for diagnosis, treatment and prevention of cancer disease. It will radically change the way we diagnose, treat and prevent cancer to meet the goal of eliminating suffering and death from cancer. Although most of the technologies described above are promising and fit well with the current methods of treatment, there are still safety concerns associated with the introduction of them in the human body. These will require further studies before some of the products can be approved. The most promising methods of drug delivery in cancer will be those that combine diagnostics with treatment. These will enable personalized management of cancer and provide an integrated protocol for diagnosis and follow up that is so important in management of cancer patients. There are still many advances needed to improve nanoparticles for treatment of cancers. Other targeted drug delivery systems mentioned above in the article such as brachy therapy ,electrochemotherapy are competent with nanoparticles in treating the cancer. Hopefully, this will allow the development of innovative new strategies for cancer cures. Although nanotechnology is still at an early stage of development, the possibilities for new therapies using this technology to treat cancer seem to be very numerous.

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