ROLE OF NANOTECHNOLOGY IN CANCER THERAPY AND DIAGNOSIS

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ABSTRACT:

In the recent times nanotechnological innovations have been applied extensively in finding solutions to problems encountered during conventional cancer therapy and diagnosis- mainly catering to drug targeting and minimizing concomitant adverse effects. From the first studies on liposome-encapsulated drug nanoparticles, progressing through PEGylation to incorporation of biomarkers on the surface, the field has continuously evolved to accommodate newer technologies like gene therapy using Rexin-G, delivering silencing RNA by "Trojan horse" approach to the tumour cells, thermal destruction of the cancerous cells using Kanzius machine and gold nanoparticles. On similar lines, semiconductor-stuffed nanoparticles called quantum dots have improved cancer detection by leaps and bounds. The field of nanotechnology continues to excite the researchers for its immense and untapped utility towards cancer therapy and diagnosis, as witnessed in form of undertrial projects like the formulation of novel BIND-014 nanoparticle, cyclodextrin-based nanoparticle, chemically engineered adenovirus-nanoparticle for stimulating the immune system and another one used as a magnetic resonance imaging contrast agent, among others. Commercialization of recyclable, microemulsion-based nanoparticles is still underway, which could possibly be a significant step towards eco-friendliness and cost reduction.

KEYWORDS: Nanoparticle, nanotechnology, carbon nanotube, cancer, tumour.

INTRODUCTION:

Cancer is one of the leading causes of death the world over, accounting for about 13% of all deaths[1]. The ongoing trend is expected to give a toll of over 11 million fatalities in 2030[1]. Cancer is a condition that is difficult to detect, check and treat. Conventional approaches of treatment include surgical removal of the diseased tissue, chemotherapy and radiation therapy, while immunotherapy and hormone therapy have also gained remedial popularity. However all these sanative methodologies are plagued with undesirable side-effects, to such an extent, that they often coerce the patients to discontinue the therapy, resulting in increasing mortalities. Thus the need of the hour is a formulation that not only minimizes or eliminates such undesirable adverse effects, but also suitably targets the drug to its requisite site of action. The answer to this comes in form of nanoparticulate drug delivery system. Nanotechnology is a multidisciplinary approach involving particles in the size range of 1-1000 nm, that are finding promising applications in the areas of cancer therapeutics and tumour imaging.

Tumour cells have a leaky vasculature, characterized by discontinuous endothelium, with gaps between the cells, of the order several hundred nanometers[2,3]. These open gaps, vesicular vacuolar organelles and fenestrations aid macromolecular transport acrfoss tumour vessels. However it is still unclear which one of these is predominantly responsible for tumour vascular hyperpermeability[4]. Tumour interstitium witnesses a high interstitial pressure and an absence of a functional lymphatic system. Thus delivery of an antitumour drug to the interstitium is not only governed by the physicochemical properties of the drug molecule, like its size, charge, configuration and hydrophobicity, but also by the properties of the interstitium like the structure, composition and

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internal pressure[5]. The cytotoxic drugs passively diffuse across the hyperpermeable blood vessels to accumulate within the cancerous tissues. The retention time of these drugs within the interstitium is seen to increase owing to compromised clearance by the impaired lymphatic system. Thus this phenomenon, known as the enhanced permeability and retention effect (EPR), results in intratumoural drug accumulation, which is higher than that observed in other tissues and plasma[6]. EPR is a characteristic of passive targeting of tumours. However, the cancer cells have an innate tendency to develop resistance against the cytotoxic drugs. This multi-drug resistance could be attributed to multiple factors operating in tandem, like the overexpression of P-glycoprotein causing efflux of xenobiotics out of the cell, together with a change in enzymatic functions and intracellular drug distribution.[7] Some agents like poly(alkyl cyanoacrylate) nanoparticles[8] and doxorubicin, a substrate for P-glycoprotein,[9] are able to overcome multidrug resistance mediated by P-glycoprotein.

The fate of any drug, when administered in vivo, depends upon a combination of various processes, grouped mainly in form of absorption, distribution, metabolism and elimination processes. Thus exercising control over one or more of these operations, mainly by altering the physicochemical characteristics of the drug, could enable to achieve the desired drug profile in vivo. Anticancer drugs, formulated as nanoparticles, are able to efficiently accumulate intracellularly, thereby enhancing antitumour efficacy. This is predominantly a result of endocytosis or phagocytosis of the drug loaded nanopaticles. The formulation of nanoparticles is brought into realization either in form of a nanosphere, comprising of a polymeric matrix, or as a nanocapsule, whereby a thin polymeric membrane encapsulates an oily or aqueous core. Polymers generally used for the purpose are poly(alkyl cyanoacrylates), poly(methylidene malonate) and polyesters such as poly(lactic acid), poly(glycolic acid), poly(e-caprolactone) and their copolymers.[10] Lipophilic drugs are more readily incorporated into nanocapsules due to their higher solubility in the polymer matrix or within the oily core, as compared to their hydrophilic counterparts, which in turn could be adsorbed onto the particle surface. Natural macromolecules, such as proteins and polysaccharides, non polar lipids, and inorganic materials like metal oxides and silica can also be used in the preparation of nanospheres.[10]

BACKGROUND:

Majority of the cancer therapeutics based on nanotechnology are described as nanovectors, which are injectable nanoscale delivery systems.[11,12] Structurally, nanovectors chiefly comprise of 3 main constituents- core material, therapeutic/imaging agent and a biological surface modification. One of the most important reasons for the popularity of nanovectors in the area of cancer therapy and imaging is their ability to get suitably modified to overcome the barriers, hampering the access of the agent to the site of action, as in case of blood-brain barrier. High-grade gliomas being extremely resistant to all forms of conventional cancer treatment pose a great challenge to the formulator and the physician in their successful mitigation.[13,14,15] Glioma cells and their neoplastic precursors have such biological and biochemical properties that enable them to evade the tumour associated host immune response and invade the surrounding extracellular areas of the brain[16,17]. Nanoparticles in combination with the Boron Neutron Capture Therapy have been useful in such cases, wherein the destructive effects of the high energy boron neutrons, concentrated within the tumour cells, have given promising results.[18]

Two prime issues concerned with the nanotechnology-based approach are the recognition of the tumour and the site-specific delivery of the therapeutic/diagnostic agent. The first studies demonstrating the use of nanovectors in cancer chemotherapy were based on the liposome-encapsulated doxorubicin, giving higher anti-tumour efficacy and reduced cardiotoxicity, when compared to the free-drug form.[19,20] Conventional nanoparticles, on entering into the blood stream tend to get rapidly opsonized and cleared by the mononuclear phagocytic system (MPS). However on introducing suitable modifications in the form of a reduction in particle size to less than 100nm and an increase in the surface hydrophilicity the nanoparticles are rendered capable of reducing clearance by the macrophages.[21] Conventional Nanoparticles are of maximum utility against Kupffer cells and other targeted macrophages, as they are easily taken up by them. However myelosuppression is a cause of major problem as these agents target the bone marrow.[22] One of the first modifications introduced within the liposome nanovectors was the use of PEGylation to bring about surface changes so that their uptake by reticuloendothelial system (RES)

is reduced but the circulation time and therapeutic efficacy are enhanced.[23] Such nanovectors demonstrating reduced recognition by phagocytes are called as sterically stabilized carriers or "stealth carriers". Besides PEG, other hydrophilic polymers used in coating the surface of conventional nanoparticles are polaxamers, polaxamine, polysaccharides etc.[24] Such nanoparticulate forms are empowered by long circulating half life and better tumour targeting, even outside the MPS.[25] Other means of selectively localizing liposome-encapsulated anti-tumour drug include incorporation of biomarkers on the surface and addition of cationic charge to the liposome, which has shown to double the accumulation of the nanovector around the vessels surrounding tumour.[26]

Nanoparticles can also be actively targeted to the tumour cells, based on the overexpression of certain specific ligands or antigens. For instance, folate receptors are overexpessed on many types of tumours. Thus folate bound to PEG cyanoacrylate nanoparticles display 10 times higher affinity for folate binding protein than the free folate form, indicating that conjugated nanopaticles could be appropriately used to establish stronger bonds with the malignant cells.[27] The cytokine CCL21 is capable of extensively attracting and activating immune cells, with a concomitant efficacious anti-tumour activity. Thus attachment of folic acid and CCL21 to bifunctional-nanoparticles, in form of chitosan coated quantum dots resulted in effective targeting of human colonic adenocarcinoma cells.[28] Similarly other ligands like tranferrin, and some specific tumour antigen, like prostrate-specific membrane antigen (PSMA) could also be targeted actively.

The materials used in the fabrication of nanoparticles are classified into carbon nanotubes, buckyballs, graphene and nanocomposites. Structurally, carbon nanotubes are composed of carbon molecules arranged cylindrically, having diameter around 1 nm.[29] The properties making them ideal for use against tumour cells are easy penetration through cell membranes, low toxicity, large surface area and biocompatibility.[30] Studies have found that nanotubes carrying drugs like paclitaxel[31] and cisplatin[32] demonstrated higher activity against the cancer cells. Additionally carbon nanotubes have a unique ability to absorb near-infrared light, to which the human body is transparent. So as they absorb the light waves, the resulting increase in temperature causes a selective destruction of the tumour cells, without affecting the surrounding healthy cells.[33,34] Graphenes are carbon sheets having large surface area that are just one atom thick, and are used as sensors in the diagnosis of diseases, by virtue of attachment of fluorescent molecules and single strands of DNA, specific for a particular disease.[35] Nanocomposites are matrix bodies wherein attempts have been made to combine magnetic and fluorescent particles in a single system to enable tumour targeting and diagnosis respectively.[36]

RECENT ADVANCES IN CANCER THERAPY USING NANOPARTICULATE SYSTEM:

The recent times have witnessed a new awakening towards exploring the indefinite opportunities associated with the application of nanotechnology in cancer therapy and diagnosis, prompting viable extensions and updating of available technologies and emergence of newer avenues in this field, as seen in case of gene therapy using Rexin-G, a nanoparticle designed to deliver a fatal gene directly into the cancer cell.[37] The ENGene IC Delivery system, commonly called as the "Trojan Horse" approach delivers a small double-stranded RNA known as short interfering RNA (siRNA) to the tumour cell and signals it to stop producing agents inducing chemotherapy resistance.[37] The gene-silencing siRNA nanoparticles, with transferrin attached to their outer surface for targeting, are injected into the bloodstream to reach the tumour cells, whose acidic environment causes the nanoparticles to release the siRNA, which in turn shuts down particular genes causing degradation of the RNA transcripts, consequently halting the multiplication of cancerous cells.[38]

Another approach, still underway, is the Kanzius Machine, conceptualized on using radiowaves to heatup and selectively destroy the cancer cells. In addition to this, another new method uses nanoparticles made up of gold, sandwiched between two pieces of iron oxide, to which antibodies specific to colorectal cancer cells have been bound. Near infrared radiations, when absorbed by the gold core of the nanoparticles result in heating up of the cancerous cells followed by their subsequent death, without affecting the nearby normal cells.[40]

Over the years it has been proven that combination drug therapy have a clear-sighted edge over single drug therapy in case of cancer treatment, but delivering the right amount of each drug to the tumour has been a challenge. A recent study has brought into realization nanoparticles that could deliver precise doses of two or more drugs to prostrate cancer cells. This novel method uses a technique whereby drug molecules are hung like pendants from polymeric units, before making the polymeric nanoparticle. Thus the formulator can precisely control the ratio of the drugs used and their rate of release from the dosage form.[41]

BIND Biosciences has initiated Phase 1, open label, Clinical Trials of BIND-014, a novel targeted nanoparticle given by IV Infusion to patients with advanced or metastatic Cancer.[42] The nanoparticle is multi-elemental in nature, with the core comprising of a matrix of docetaxel and a biodegradable polymer, polylactic acid, which gives an extended release profile to the drug. This drug-filled core is then covered with a "stealth coating" of polyethylene glycol, which prevents the particle's macrophageal recognition and subsequent degradation. A final coating of targeting ligands specifically bind the molecule to prostate-specific

Table 1: COMPANY DIRECTORY

COMPANY	PRODUCT
American Elements	Nanoparticles and Quantum Dots
Abraxis BioScience	Nanoparticles composed of albumin for targeted delivery of drugs to tumors
Calando Pharmaceuticals	Nanoparticles for the targeted delivery of siRNA to cancer tumors
CytImmune	Gold nanoparticles for targeted delivery to tumors
Evident	Quantum Dots
Epeius Biotechnologies	Nanoparticles for targeted delivery of drugs to tumors
Invitrogen	Quantum dots for medical imaging
MagArray	Diagnostic testing using magnetic Nanoparticles
MagForce	Iron oxide nanoparticles used in heat treatment of solid tumors
Nanospectra Biosciences	Auroshell ™ particles (nanoshells) for thermal destruction of cancer tissue
Nanobiotix	nanoparticle nbtxr3 when activated by x-rays, generate electrons that cause the destruction of cancer tumors
Nanocs	Gold and silver Nanoparticles
Nanosphere	Diagnostic testing using gold nanoparticles to detect low levels of proteins indicating particular diseases
NanoBioMagnetics	Magnetic nanoparticles for targeted drug delivery and other applications
Oxonica	Diagnostic testing using gold Nanoparticles as biomarkers
T2 Biosystems	Magnetic Nanoparticles for diagnostic testing

membrane antigen (PSMA), found on prostate cancer cells.[43,44]

Polymeric nanoparticles stuffed with even smaller sized particles of semiconductors, called quantum dots, may prove to be a benchmark in cancer diagnosis. These coated nanoscale semiconductor crystals act as coloured light sources whose color depends solely on particle size. When linked to a molecule capable of binding to a substance of interest, quantum dots act like a beacon that lights up when binding occurs. Thus quantum dots can be used to create assays for detecting multiple substances simultaneously, e.g., serum levels of the breast cancer marker Her-2, actin, microfibril proteins, and nuclear antigens can be easily detected simultaneously[45].

Yet another development in the field has been made by the Institute for Medical Science and Technology, at Dundee and St Andrews universities, via the Ninive project (Non Invasive Nanotransducer for *In vivo* gene therapy), wherein multi-walled carbon nanotubes are designed in a novel way to mimic a biological virus.[46] Each nanotube carries a drug on its surface and is able to penetrate into a specific cell type like a nanosized needle. On reaching their target site, a pulse of microwaves from the outside causes them to shed their loads inside the cells. The nanotubes are so coated to make them bio-compatible.[47]

Tumor-targeted liposomes delivering high concentrations of boron to brain tumors for boron-neutron capture therapy are another milestone in the realm of tumour targeting. The delivery vehicle consists of PEG-coated liposomes loaded with sodium borocaptate. A tumor targeting agent, transferrin, is bound to the PEG coating. Finally boron is loaded into liposomes coated with PEG. Such a complex, when irradiated with neutron, proves to be fatal to the target tumour cells.[48]

Following is a list (Table 1) of some companies marketing various nanoparticulate formulations within the realm of cancer therapeutics and diagnosis.

FUTURE TRENDS:

Nanopaticulate drug delivery system appears to be a promising new direction in cancer cell therapy, owing to the fact that it provides adequate flexibility to the formulator in respect of designing and tuning properties. Some of the research works still underway in different stages of clinical trials include chemically engineered adenovirus-nanoparticle stimulating the immune system[49], a cyclodextrin-based polymer conjugated to camptothecin for solid tumours[49] and a nanoparticle based magnetic resonance imaging contrast agent that binds to the protein αvβ3-integrin, found on newly developed vessels associated with tumour development[50], among others. Moreover recovering and reusing pricey nanoparticles, particularly gold nanoparticles, could help in bringing down the expenditure considerably, especially when it is known that nanoparticles form complex, difficult-to-separate mixtures with other substances. Recently it has been demonstrated on a laboratory-scale that microemulsions using cadmium and zinc nanoparticles could be separated into two layers when heated. While one layer containing nanoparticles, in their original shape and chemical properties could be easily recovered, the other could be discarded[51].

SUMMARY:

Nanooncology has emerged as a promising avenue in the detection, mitigation and treatment of tumour cells and is looked upon by the researchers to come up with breakthrough technologies in the field. The use of nanotechnology has introduced greater flexibility in the paradigm of cancer therapeutics and diagnostics by not only improving the efficacy, safety and tumour-targeting but by also aiding in the reduction of the adverse effects, invasiveness and risks associated with conventional drug therapy. However a deeper understanding of the underlying mechanisms of tumour development is required to suitably develop a rational design of optimized nanoparticles for better cancer cells targeting and treatment.

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