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Review Article

CANCER NANOTECHNOLOGY: NANOPARTICULATE DRUG DELIVERY FOR THE TREATEMENT OF CANCER

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ABSTRACT

In 21st century scientist all around are trying to formulate the new drug delivery with better efficacy and effectiveness to treat cancer. So their focus has been shifted toward the Nano based drug delivery system because nanotechnology plays with the dimension of the matter typically on the 0.2- to 100-nm scale (Nano scale). When the matter is size reduced its properties changes this is because at the Nano scale the percentage of atoms at the surface of a material becomes more significant. The interesting part of nanotechnology is that when the matter is in bulk possess relatively constant physical properties regardless of their size, but at the Nano scale the matter behave in the different ways. This is because when the material becomes smaller the percentage of atoms at the surface increases relative to the total number of atoms of the material bulk. This can lead to unexpected properties of nanoparticles which are partly due to the surface of the material dominating over the bulk properties. Hence nanotechnology is playing a important role in developing better and effective drug delivery system to fight against cancer.

Keyword: Cancer nanotechnology,

INTRODUCTION

Over past many year there has been an increasing demand of developing new delivery systems by pharmaceutical scientists, physicians and other scientists related to the health field. Drug delivery is an interdisciplinary area of research that aims to make the administration of complex drugs feasible. So the main aim in developing new drug delivery system is to deliver the drug to the desired tissue in the human body so that it increases the effectiveness of the treatment and minimizing the side effects associated with the drug. Micro and nano drug delivery systems are developed for these purposes especially to target the drugs to a specific area or organ in a more stable and controlled way.

Contemporary cancer therapy, particularly with respect to drug delivery, has begun an evolution from traditional methodology. Part of this change is based on the need to increase the therapeutic index of chemotherapy drugs. Although cancer cells are inherently more vulnerable than normal cells to the effect of chemotherapy agents, the drugs are nonselective and can cause injury to normal tissues. Indeed, it is toxicity of normal cells that constrains dose and frequency both important factors in the persistence of cancer cells after completion of chemotherapy treatment. Attempts are now focused on efforts to kill cancer cells by more specific targeting (and delivering the therapeutic agent to tumor cell only) while sparing normal cells. To achieve these goals, the focus is the development of novel carriers for both existing and new drugs and defining better therapeutic targets relative to the molecular changes in the cancer cells, their vasculature, and the related stroma.

Importance of nanotechnology in cancer research

Nanotechnology involves the application of scientific knowledge from a variety of disciplines in science and engineering to understand, manipulate, and control the properties of matter at nanoscale (1–100 nm) size dimensions [1]. Nanotechnology holds tremendous potential for overcoming many of the problems that conventional methods face in the treatment, diagnosis and detection of cancer [2]. In particular, nanoparticles (nanoscale-sized particles) have been developed and investigated for cancer diagnostics and therapeutics (NP-CDTs). Pre-clinical studies have shown that these NP-CDTs offer many advantages over small-molecule approaches. For example, NP-CDTs can ameliorate the problems of the poor *in vivo* bio distribution and adverse side effects associated with small-molecule agents (e. g., drugs, image contrast agents, etc.). These problems arise due to lack of specificity of the agents in targeting cancer cells and are due to a range of effects such as: rapid uptake by the reticuloendothelial system (RES); clearance by the macrophages in MPS (Mononuclear Phagocyte System) organs, if the intended target cells are not located in the MPS organs; and the presence of barriers (e. g., blood–brain barrier (BBB) [3]. Cancer cells share many features with normal cells, and therefore, agents lacking the desired target specificity will also target healthy normal cells and damage them, there by, causing adverse side effects in the body. In drug delivery, poor bio distribution of the drug can result in low drug concentration levels at the tumor site. These low concentration levels, in conjunction with dose-limiting toxic side effects, reduce the drug's overall therapeutic efficacy. NP-CDTs can increase the circulation times and efficacy of therapeutic and diagnostic agents [2–5]. Generally, circulation times increase if the agent of interest is attached to a small, hydrophilic nanoparticle [6]. While small sizes reduce the likelihood of uptake by the RES, hydrophilicity increases the overall solubility of the diagnostic/ therapeutic agent. In addition, functionalized nanoparticles target specific receptors that are over-expressed on surfaces of cancer cells, and this in turn facilitates the uptake of drug-loaded nanoparticles via endocytic pathways [2–5]. In the year 2005, the FDA (Food and Drug Administration) approved a paclitaxel-loaded albumin nanoparticle formulation for the treatment of metastatic breast cancer [7] – a positive advance for the therapeutic use of NP-CDTs. Additionally, several other NP-CDTs are being evaluated in clinical trials [8].

Tumor cells and their environment

An overview of the tumor microenvironment and the tumor cell helps to elucidate the problems of drug delivery in cancer.

(a) Tumor vasculature

A tumor cell mass obtains nutrients for growth by passive diffusion until it reaches a size of about 2 mm^3 [9]. To continue growth, new blood vessel formation (angiogenesis) must develop to supply nutrients to the expanding tumor mass. A variety of biologic signals initiate tumor angiogenesis but the process is not orderly and tumors have poorly vascularized areas with resultant necrosis; and, poor drug distribution occurs in these areas, other areas of the tumorare richly vascularized. Importantly, tumor vessels are abnormal and have aberrant branching blind loops and tortuosity. Tumor vessels are leaky due to basement membrane abnormalities and to decreased numbers of pericytes lining rapidly proliferating endothelial cells [10]. This results in enhanced permeability for

molecule passage through the vessel wall into the interstitium surrounding tumor cells. The size of the gaps between the leaky endothelial cells ranges from 100 to 780 nm depending on the tumor type [11–13]. This is in contradistinction to the tight endothelial junctions of normal vessels typically of 5 to 10 nm size.

(b)Tumor interstitium

The tumor interstitium is composed of a collagen network and a gel like fluid which has high interstitial pressures offering resistance to the inward flux of molecules. Transport of drugs into the interstitium is determined by the balanced force between the outward interstitial pressure and the properties of the diffusing drug including particle size and configuration, hydrophobic nature and electrical charge. Tumor interstitial pressures are higher in the tumor center and lower in the periphery, favoring decreased drug diffusion to the center of tumors [14, 15]. Additionally, tumors lack well-defined lymphatic networks. Hence, drugs that gain interstitial access may have extended retention times in the tumor interstitium. This feature is termed the enhanced permeability and retention (EPR) effect and favors tumor interstitial drug accumulation [16, 17].

Major mechanisms of anticancer drug resistance

The major modalities of antitumor drug resistance may be grouped into at least five categories: decreased drug influx, increased drug efflux predominantly via ATP-driven extrusion pumps frequently of the ATP-binding cassette (ABC) super family, activation of DNA repair, metabolic modification and detoxification as well as inactivation of apoptosis pathways with parallel activation of anti-apoptotic cellular defense modalities [18-21]. Members of the ABC super family including P-glycoprotein (P-gp/ABCB1), multidrug resistance proteins (MRPs/ABCC) and breast cancer resistance protein (BCRP/ABCG2) function as ATPdriven drug efflux transporters, which form a unique defense against chemo therapeutics and numerous endo-and exotoxins.

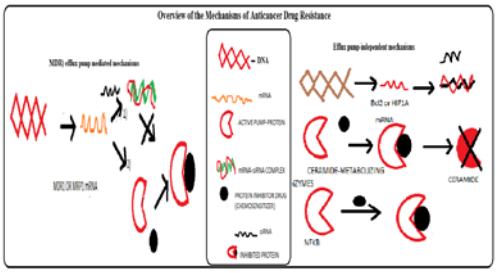

Fig. 1: Overview Diagram of the mechanisms of anticancer drug resistance (A) Multi drug resistance (MDR) effluxpump mediated mechanisms may be suppressed by (a1) Inhibiting translation of mRNAs to MDR efflux pump proteins such as MDR1 or MRP1 using siRNA (a2) Chemical inhibition of MDR efflux protein by a chemosensitizer (e. g. verapamil).(b) (B) Efflux pump-independent mechanisms may be suppressed by (b1) siRNA inhibiting translation of Bcl2 or H1F1A mRNA, (b2) targeting ceramide-metabolizing enzymes, inhibiting the synthesis of ceramide, or (b3) inhibiting the function of the transcription factor NF-*k*B

These pumps significantly decrease the intracellular concentration of a multitude of endogenous and exogenous cytotoxic agents which are structurally and mechanistically distinct, thereby resulting in Multi drug resistance (MDR). Among the mechanisms of drug resistance, that are independent of drug efflux pumps, a prominent role is played by the activation of anti-apoptotic cellular defense modalities, including the over expression of BCL2, a pro-survival, anti-apoptosis regulator and nuclear factor kappa B (NF-kB), a master transcription factor which controls the expression of various genes including those involved in suppression of the apoptotic response [22]. NF-kB is a heterodimeric protein composed of different combinations of members of the Rel family of transcription factors. Targeting cellular death pathways including apoptosis is a promising strategy for cancer drug discovery. To date, at least three major types of cell death mechanisms have been distinguished: apoptosis, autophagy, and necrosis [23-25] and more than 50% of cancers have defects in the apoptotic machinery. Among the best characterized of these abnormalities are the increased expression of the BCL2 family proteins and mutations in the tumor suppressor p53 gene. While BCL2 family members have at least one conserved BCL2 homology domain, the pro-survival members of the BCL2 family (BCL2, BCLxL, BCL-w, MCL1, A1 and BOO/DIVA) have as many as four BCL2 homology domains, which are involved in the regulation of cell survival via protein–protein interactions. NF-kB is ubiquitously expressed in almost all animal cell types and is involved in cellular responses to stimuli such as stress, cytokines, free radicals, ultraviolet irradiation, oxidized LDL, and bacterial or viral antigens. Conversely, impaired regulation of NF-kB (i.e. activation) and hence chronic inflammation have been recently shown to result in malignant transformation, autoimmune diseases, septic shock, viral infection, and improper immune development [26-27]. Nano-medicines targeting these various drug resistance mechanisms in cancer cells *in vitro* and *in vivo* as well as in clinical trials as depicted in fig. 1 [28].

Types of Nano vehicles currently used for delivery of chemotherapeutics

The promise of nanotechnology lies in the ability to engineer customizable nanoscale constructs, that can be loaded with one or more payloads such as cancer chemotherapeutics, chemosensitizers or imaging-aid components [29]. Moreover, these rationally designed nano vehicles may be equipped with an active targeting element for enhanced selectivity, such as the B9 vitamin, folic acid (FA), which targets with high affinity, and hence selectivity, folate receptors (FRs). FRs were found to be over expressed on the cell surface of various carcinomas including ovary (nonmucinous), endometrium, breast, colon, lung, kidney, bladder and pancreas [30-32].

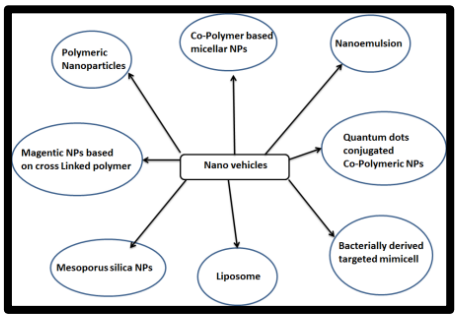

Fig. 2: Schematic summary of drug delivery vehicles currently used for the delivery of anticancer drug resistance combination therapy (selected examples): (a) Polymeric NPs, e. g. chitosan-based [33-34]. (b) Co-polymer based micellar NP, e. g. pluronic F127 [35]. (c) Micro-or nanoemulsion-based nanovehicles [36]. (d) Quantum dot-conjugated co-polymeric NP [37]. (e) Liposomes [38]; Zhu et al., 2009)[39]. (f) Bacterially derived minicells [40]. (g) Metallic or magnetic polymeric NPs [41]. (h) Mesoporous silica NPs [22]

It has been recently demonstrated the selective targeting and cytotoxicity of a FA-and methotrexate (MTX)-conjugate of arabinogalactan to FR alpha-over expressing cells, compared to counterpart cells lacking FR alpha expression [42]. In addition, selective cytotoxicity was obtained by a target-activated release mechanism, based on an endosomally cleavable tetrapeptide, Gly-Phe-Leu-Gly, connecting MTX to the polysaccharide nanovehicle.

When designing a drug delivery vehicle, a variety of factors must be taken into consideration including the degree of complexity of its preparation and the cost of nanovehicle formation, the qualitative and quantitative loading capacity of the different therapeutic cargos, the stability of the loaded NPs in solution prior to use, the half-life in the circulation, its bio accessibility to the target tissue, the selectivity of its bio-distribution, the extent of drug release and desired effect at

the destination, and finally its biological fate, i.e. accumulation or degradation and clearance, which must be determined via detailed pharmacokinetic and pharmacodynamic studies.

Various nanovehicles are described in the literature that were specifically designed to overcome anticancer drug resistance, each of which bears its advantages and caveats regarding the strict considerations delineated above. The drug cargo is usually released from the nanovehicle either extra cellularly in the tumor or in the tumor micro environment, i.e. the stroma and vasculature supporting the cancer cells, or intra cellularly typically through cellular uptake via receptor-mediated endocytosis [32]. An area of intense research currently focuses on stepwise delivery into intracellular compartments, primarily the nucleus [43-45], which contains the target of many small molecule anticancer drugs.

When designing a drug delivery system with a selective target-activated release mechanism, one should consider the drug administration route, and the path of the drug(s) to the target cells, with respect to the physico-chemical and biological conditions (e. g. pH, ionic strength, enzymes present, and serum albumin entrapment) and the barriers encountered (e. g. blood vessel endothelium such as blood–brain barrier, cell membrane, nuclear membrane and nuclear pores).

In the case of extracellular release, the drug delivery system is designed to liberate the drug(s) under the extracellular environment conditions in the target tumor or its microenvironment, and the drug has to be able to penetrate the cell membrane either passively by diffusion, or actively by specific transporters, or via receptor-mediated endocytosis.

In the latter case, the drug delivery vehicle carrying the drug cargo has to enter the cell in an intact form, yet this drug payload must be successfully liberated in its active form under the harsh lysosomal conditions (e. g. acidic pH, various hydrolytic enzymes), which then must diffuse or be transported into the cytosol.

The various drug delivery systems are presented in fig. 2. Although, to the best of our knowledge, there are currently no reports of NPs for the delivery of drug combinations aimed at overcoming drug resistance which have been clinically tested, various nanovehicles for targeted delivery of anticancer drugs have already undergone *in vivo* testing in mouse models and clinical evaluation in man. Several of these studies have used serum albumin-based NPs as carriers [46-51], and some of these studies have already reached phase II of clinical evaluation [47-51]. The natural role of serum albumin as a systemic vehicle for binding and delivering small molecules, makes it a useful component of NP delivery systems. Following the success of Doxil, a pegylated (polyethylene glycol coated) liposome-encapsulated form of doxorubicin, approved by the FDA for the treatment of ovarian cancer and multiple myeloma, liposomes (fig. 2e) are also extensively studied for various therapeutic applications [38-39]. Carbon nanotubes have also found potential application in drug delivery [54]. An important class of nanovehicles encompasses polymeric NPs (fig. 2a) including block-copolymericmicellar NPs [35, 52] (fig. 2b). The combination of diagnostic imaging aids along with therapeutics loaded onto the same NP system known as "theragnostic NPs" 56], is a new and promising route of drug delivery that is attracting intensive research and development for both cancer diagnostics and anticancer therapeutics. Magnetic NPs such as the thermo-sensitive magnetoliposomes studied by Zhu et al. (2009)[39], are another interesting class of nanovehicles with potential theragnostic capabilities (fig. 2g). As aforementioned, FA conjugates for specific targeting of various carcinomas that highly over express FRs are among the most elegant targeting strategies, harnessed for various types of NPs [31, 32]. Table 1 summarizes selected examples of reported *in vivo* evaluation and clinical trials of such nanovehicles, and lists their main components as well as their targeted tumor type and the mode of administration.

Tabel 1: Selected examples of nanoparticles for cancer targeting recently evaluated *in vivo* and in clinical trials

Nano vehicle	Main bioactive or cytotoxic cargo	Combined or sequential treatment with	Tumor type	Administration mode	*In vivo* /clinical trial stage	Reference
Albumin bound nanoparticles	Paclitaxel	-Lapatinib	-Advanced solid malignancies	-Intravenous (IV)	Phase I	Chien et al. (2009)
		5-Fluorouracil/ epirubicin/ cyclophosphamide	-Breast cancer	-IV	Phase II	Robidoux et al. (2010
		-Gemcitabine	-Non-small cell lung cancer and small cell lung cancer; metastatic breast cancer	-IV	PhaseI; Phase II.	Stinchcombe et al. (2008) and Roy et al. (2009)
			-Epithelial cancer of the ovary, fallopian tube, and peritoneum	-IV	PhaseII	Teneriello et al. (2009)
		-Carboplatin/ trastuzumab	-HER-2 overexpressing metastatic breast cancer	-IV	PhaseII	Conlin et al. (2010)
Polybutylcyanoacrylate NPs	Mitoxantrone	--	Hepatocellular carcinoma	IV	PhaseII	Zhou et al. (2009)
Cyclodextrin-containing linear polymer, decorated with PEG and transferrin	RNAi	--	Solid melanoma tumors	IV	PhaseI	Davis et al. (2010)
Liposome	9-Nitrocamptothecin and cisplatin	Doxorubicin	Primary and metastatic lung cancer	Aerosol	PhaseI	Gagnadoux et al. (2008)
Folate–hapten conjugate	Hapten	--	Mice liver	IV	*In vivo* and Phase II	Low et al. (2008)
Thermo-sensitive	Methotrexate	--	Skeletal muscular	IV	*In vivo*	Zhu et al.

magneto-liposomes			tissue			(2009)
Single wall carbon nanotubes	Paclitaxel	--	Murine 4T1 breast cancer	IV	*In vivo*	Liu et al. (2008)
Pluronic F127 polymer nanocrystals	Paclitaxel and camptothecin	--	Murine breast cancer	IV and Oral	*In vivo*	Liu et al. (2010)
Aerosol-OT (surfactant) (AOT), and sodium alginat	Doxorubicin	Photodynamic therapy using methylene blue	Balb/c mice bearing Drug resistant syngeneic JC tumors (mammary adeno-carcinoma)	IV	*In vivo*	Khdair et al. (2010)

Nanoparticles in clinical use

Despite extensive research and development, only a few drug delivery nanoparticles currently are FDA approved and available for cancer treatment. Liposomal anticancer drugs were the first to be approved for therapy in cancer. Two commercial liposomal formulations are available in the United States. These are pegylated liposomal doxorubicin (Doxil in the U. S. and Caelyx outside the U. S.) and liposomal daunorubicin (DaunoXome). A third liposomal formulation approved in Europe is nonpegylated liposomal doxorubicin (Myocet). Adding to this formulary, an albumin bound paclitaxel nanoparticle Abraxane was recently approved by the FDA for the treatment of breast cancer.

Liposomal anthracyclines

The available liposomal formulations represent encapsulated anthracyclines— doxorubicin in Doxil and Myocet and daunorubicin in DaunoXome. While anthracyclines are highly active cytotoxic drugs, they have significant toxicity associated with their use both acute and cumulative. High peak plasma concentrations of anthracycline are associated with risk for congestive cardiomyopathy as is the lifetime cumulative dose of the drugs. By liposomal encapsulation, the anthracycline pharmacokinetics are altered and cardiac risk is decreased, but not eliminated [57-58]. Additionally, anthracycline toxicity to normal tissue, including alopecia and myelosuppression, are reduced by liposomal encapsulation.

Pegylated liposomal doxorubicin (Doxil)

Doxil particles are small (<100 nm) unilamellar vesicles with encapsulated doxorubicin precipitated in the liposomal vesicle by an (NH_4) SO_4 gradient [59]. The polyethylene glycol coating (pegylation) prevents opsonization and avoids RES clearance. It also adds steric stabilization to prolong the plasma $t_{1/2}$. After extravasation through tumorendothelium, Doxil liposomes disintegrate and deliver doxorubicin. Drug concentration has been measured at 10-fold higher in tumor tissue compared with conventional free drug administration [60]. The recommended systemic dosage for Doxil is 40 to 50 mg/m^2 infused over 1 hour every 4 weeks. The main toxicities are palmar plantar skin reactions (PPE) and stomatitis/mucositis. Compared with a conventional doxorubicin infusion,

Doxil has less cardio toxicity, myelosuppression, alopecia, nausea, and vomiting. The FDA approved three major indications for pegylated liposomal doxorubicin—AIDS related Kaposi's sarcoma, platinum pretreated ovarian cancer, and first line monotherapy of metastatic breast cancer.

Clinical trials of pegylated liposomal doxorubicin in breast and ovary cancer and Kaposi's sarcoma

(a) Breast cancer

Women with previously untreated metastatic breast cancer were randomized to receive pegylated liposomal doxorubicin (PD) at 50 mg/m^{2}every 4 weeks or doxorubicin (D) at 60 mg/m^{2}every 3 weeks [57]. Response rates, progression free survival, and overall survival was not statistically significant between the two arms. However, toxicity profiles of the two drugs were different. PD had more skin toxicity and stomatitis/mucositis whereas D had more neutropenia and nausea/vomiting. Cardiac safety profiles favored PD with higher rates of cardiac toxic effects in patients receiving D. Doxorubicin patients experienced greater declines of left ventricular ejection fraction measured by serial multiacquisitiongated scans and were more likely to have clinical symptoms of congestive heart failure.

(b) Ovarian cancer

Women with pre treated ovarian cancer who failed or recurred on platinum based therapy were randomized to receive PD at 50 mg/m^{2}every 4 weeks or Topotecan (T) at 1.5 mg/m^{2}on day 1 to 5 every 3 weeks [61]. Response rates and progression free survival were not statistically different between the two study arms. Patients still sensitive to platinum had longer progression free survival and overall survival if treated with PD. Toxicity profiles were different, with PD having greater rates of stomatitis and skin toxicity. Topotecan-treated patients had greater rates of hematologictoxicity including grade 3 and grade 4 leucopenia and thrombocytopenia requiring dose reduction and growth factor support.

(c) Kaposi's sarcoma

Two trials evaluated the efficacy of PD in Kaposi's Sarcoma (KS) [62-63]. Each trial randomized patients betweenPD and a conventional multidrug regimen. In each study, overall response rates were statistically higher for PDand PD treated patients experienced greater symptom relief from pulmonary disease and skin lesion improvement.

Pegylateddaunorubicin (DaunoXome)

Due to the relative stability of daunorubicin in aqueous solution, the drug is encapsulated in a small unilamellarliposome (45 nm size). The NP has delayed opsonization and escapes rapid RES clearance resulting in a markedly increased AUC compared to conventionally administered daunorubicin [64]. The main toxicity observed for this drugis myelosuppression. The FDA approved indication for pegylated daunorubicin is for the treatment of Kaposi's sarcoma. A Phase III trial randomized chemo naïve Kaposi's sarcoma patients to pegylateddaunorubicin vs. a modifiedadriamycin/ bleomycin/ vincristine (ABV) regimen [65]. Overall response rates and median survival were not different between the two groups. Toxicities differed significantly with more grade 4 neutropenia for pegylateddaunorubicinand greater alopecia and neuropathy for ABV.

Nanoparticle-albumin conjugates nab-paclitaxel Abraxane

The taxanes are a family of tubulin stabilizing agents highly active and widely used in a variety of solid tumors including urologic malignancies. Paclitaxel and docetaxel are the commercially available taxanes for clinical treatment. Both of these drugs are hydrophobic and, due to solubility problems, are formulated with a solvent paclitaxelwith Cremophor-EL a polyethylated castor oil and Tween-80 a polysorbate ethanol for docetaxel. These solvents can cause severe hypersensitivity reactions and toxic tissue side effects. Patients must be premedicated with steroids and antihistamines prior to drug infusion. For paclitaxel, the drug must also be slowly infused over several hours. To decrease the toxic effects associated with these drugs, a nanoparticle formulation has been developed for paclitaxel. The technology for particle formation involves a proprietary process that binds unmodified albumin to the

paclitaxel molecule yielding a nanoparticle of 130 nm size. After infusion, these particles rapidly dissociate to yield an albumin bound

drug complex. Albumin paclitaxel molecules bind to an albumin receptor (gp60) on endothelial cells that transports the hydrophobic paclitaxel into the extravascular space. The albuminreceptors (gp60) cluster on endothelial surfaces and associate with caveolin-1, leading to the formation of a caveolae that is released into the extra vascular space. Therefore, caveolae are a major transport mechanism for nab-paclitaxel [66–68].

A second proposed transport pathway for the nanoparticle is via secreted protein acidic rich in cysteine (SPARC). Other names for this protein are BM40 and osteonectin. SPARC expression has been reported in many solid tumors including bladder and prostate cancers and is associated with a poor prognosis [69-70]. SPARC protein can bind albumin and can increase the concentration of the albumin bound paclitaxel particle in the tumor due to such binding. Hence, SPARC protein represents another transport mechanism for nab-paclitaxel into tumor cells [71]. Based on these properties, a nab-paclitaxel infusion leads to a 33% increase in intratumoral concentrations and a 50%higher dose of paclitaxel delivered compared with a conventional paclitaxel infusion; and, since nab-paclitaxel is solvent free, the infusion time is 30 minutes compared with the 3-hour infusion for conventional taxol, and no premedication is required [72]. The FDA approved nab-paclitaxel for metastatic breast cancer therapy after failure of combination chemotherapy or relapse within 6 months of adjuvant chemotherapy. A pivotal Phase III trial of 460 women compared nab-paclitaxel

with conventional paclitaxel on a 3-week schedule [73]. All patients were taxane naïve. Overall response rates were significantly higher for nab-paclitaxel 33% vs. 19% and time to progression significantly longer 23 weeks for nabpaclitaxelvs. 17 weeks. Overall survival was not significantly different for all patients. Toxicity profiles differed with nab-paclitaxel having less neutropenia compared to taxol but more grade 2 and 3 sensory neuropathy. To further explore issues of tolerance and dose response for this drug, a weekly infusional schedule has been studied and reported lower rates of neutropenia and neuropathy [74]. All patients in this trial had previously been treated with paclitaxel, docetaxel, or both drugs, and were refractory. The observed response rates for the weekly nab-paclitaxelsuggested that the drug was non-cross resistant for taxane refractory patients. This concept has particular implications for urologic cancers, notably prostate, a malignancy in which the only proven agent to prolong survival is a taxane. Nab-paclitaxel represents an alternative treatment option for such cancer patients treated with conventionaltaxanes who develop resistance or toxicity intolerance.

Nanoparticle drug delivery in urologic cancers

Currently there are no FDA approved and commercially marketed nanoparticle drugs for clinical use in urologicmalignancies. However, a variety of provocative NP constructs targeting urologic cancers are in development and inclinical trials. The design of these drugs incorporates the same principles of targeting and drug delivery discussedpreviously.

Nab-paclitaxel nanoparticle albumin conjugateAbraxane

Clinical trials have established the efficacy of the taxanes for the treatment of hormone refractory prostate cancer(HRPC) [75-76]. However, once taxane-treated and taxane-resistant, there is no proven second line therapeutic agent. Since the breast cancer trials demonstrated nab-paclitaxel's non-cross resistant activity in taxane refractory patients, this molecule becomes an ideal candidate for second line salvage therapy in prostate cancer. In addition, prostate cancer cells often over express SPARC protein, a proposed targeted carrier for delivery of albumin bound paclitaxel into cancer cells. These features of nab-paclitaxel make it a very attractive agent for use in prostate malignancy and Phase II clinical trials are currently under way.

Docetaxel encapsulated nanoparticle aptamerbioconjugate

This docetaxel encapsulated nanoparticle with the copolymer poly (D, L-lacti-co-glycolic acid) block-poly (ethyleneglycol) (PLGA-b-PEG) is surface targeted to the extracellular domain of prostate specific membrane antigen(PSMA) by the conjugation of an RNA aptamer. The aptamer binds to PSMA on the surface of LNCaP prostateepithelial cells and then is internalized into the cell. As a result, enhanced cellular toxicity is noted compared with the same NP lacking aptamers. Cell line and mouse xenograft studies of this molecule suggest great potential for therapeuticapplication in humans [77]. The technology supporting the molecule design included

utilizing biocompatible and biodegradable polymers with established safety for human use. The polymers allow sustainedintracellular drug release. The RNA aptamer is an oligonucleotide capable of binding to the target antigenPSMA with high affinity and specificity. While similar to antibodies, aptamers are nonimmunogenic, stable at wideranges of temperature and pH, and can be produced without product variability. With the polymer coat, the NP escapes rapid RES clearance. Finally, the choice of docetaxel utilizes a cytotoxic drug already proven in clinical trials to prolong survival of hormone resistant prostate cancer in humans.

Transferrin receptor targeted drug delivery system

This approach to drug delivery was developed in a murine model of prostate cancer. Nanoparticles of encapsulatedpaclitaxel with surface conjugated transferrin deliver higher paclitaxel doses into the tumor over a sustained time period compared with conventional paclitaxel delivery. The NP avoids use of the paclitaxel requiring vehicle of Cremophor-EL and its related toxicities, while targeting prostate cancer cells with up-regulated transferrin receptors [78].

Folate receptor targeted drug delivery

A pegylated lipid based NP with a conjugated folate ligand has been developed for targeted drug delivery of asuicide gene to prostate cancer xenografts from LNCaP and PC-3 cell lines [79]. This NP delivers a *Herpes simplex*virus thymidine kinase (HSV-tk) gene that phosphorylates a pro-drug ganciclovir to a toxic triphosphate, which blockscellular DNA synthesis. The drug has high transfection efficacy and antitumor activity. The particle binding appears to be to the extracellular domain of the PSMA receptor and enters the cell by endocytosis. PSMA is an important therapeutictarget because of its expression on both prostate cancer cells and the endothelial cells lining tumor vasculature. Thus, the prostate cancer cell and its sustaining vascular network become the target for suicide gene delivery.

CONCLUSION

Current available cancer therapeutic strategies suffer from severe limitations which frequently result in treatment failure. The underlying basis for such failure is multifactorial including nonspecific biodistribution and insufficient targeting of the therapeuticagents, lack of water solubility, poor oral bioavailability, low therapeutic indices, dose-limiting toxicity to healthy tissues, and most importantly, almost invariably emerging drug resistance. Drug resistance continues to be a primary hindrance for the efficiency of cancer chemotherapy.

Novel cancer nanotherapeuticsare rapidly evolving and are being implemented to overcome some of thes elimitations. To improve the biodistribution of antitumor agents, NPs have been designed for optimal size and surface characteristics in order to increase their circulation time in the bloodstream. They are able to carry and deliver their active drug payloads to cancer cells, by passive targeting mechanisms, such as the EPR effect as well as by active targeting mechanisms using ligands directed against selected determinants differentially over expressed on the surface of tumor cells. Drug resistance that impedes the efficacy of conventional chemotherapeutic agents might be overcome using rationally designed NPs.

CONFLICT OF INTERESTS

Declared None

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