

Nano Chemotherapy: An Emergent Anti-Cancer Modality

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Abstract

The notion that even relatively indiscriminate cytotoxic agents discovered largely by accident would cure cancer continues to captivate oncology. Thus, with a three-drug cocktail called BVP (bleomycin, vinblastine, cisplatin abbreviated P for platinum), metastatic testes cancer can be cured, and a high-dose cocktail of seven drugs can cure Burkitt's lymphoma. From there, an avalanche of such drugs have poured in: taxol, Adriamycin, etoposide, bleomycin (an antibiotic), and an alphabet soup of other combinations (ABVD, BEP, C-POMP, ChlaVIP, CHOP, ACT). Yet, despite these successes and the escalation of drugs and doses, the efficacy of the drug regimen remains minimal. The pattern repeats itself regularly for many forms of cancer. Fortunately, through the ability of nano particles and the nano devices that deliver these drugs more efficiently and more judiciously at tumor sites, nano chemotherapy (NCT) is evolving as an emergent, viable anti-cancer modality that builds upon and supplements conventional chemotherapy. This article introduces NCT and discusses the several nano particles and the nano devices delivering them that have been found useful. The clinical advantages of this novel strategy are outlined as well as ways of overcoming multi-drug resistance. However, like for any anti-cancer modality, toxic effects may be lurking in the background and are briefly considered.

Abbreviations: BBB: Blood Brain Barrier; BVP: Bleomycin + Vinblastine + Cisplatin; CNS: Central Nervous System; CNT: Carbon Nano Tubes; CSC: Cancer Stem Cells; CUR: Curcumin; DDP: Cisplatin; Docetaxel; DOX: Doxorubicin; DTX: Docetaxel; END: Engineered Nanoscale Device; FDA: (U.S.) Food and Drug Administration; IR: Infra-Red; LPN: Lipid-Polymer Hybrid NanoParticles; mCRPC: Metastatic Castration-Resistant Prostate Cancer; MDR: Multi-Drug Resistance; MP: Micro Particles; MRSA: Methicillin-Resistant *Staphylococcus Aureus*; NCT: Nano Chemo Therapy; NM: Nano Materials; NP: Nano Particles; OPN: Osteopontin; OS: Osteosarcoma; PNP: Polymeric Nano Particles; PLGA: poly(lactic-co-glycolic acid).

Diseases Listed: Cancers: Breast; Colon; Gastro-Intestinal; Glioblastoma; Leukemia (acute, chronic); Lung; Lymphoma (Hodgkin; non-Hodgkin); Melanoma; Myeloma (single, multiple); Osteosarcoma; Ovary.

Drugs Cited: Adriamycin; Bevacizumab; Bleomycin; Busulfan; Capecitabine; Carboplatin; Carmustine; Cetuximab; Chlorambucil; Cisplatin; Curcumin; Cyclophosphamide; Cytarabine; Dactinomycin; Daunorubicin; Docetaxel; Doxorubicin; Epirubicin; Erlotinib; Etoposide; Fludarabine; Lomustine; Gemcitabine; Getifinib; Idarubicin; Imatinib; Methotrexate; Mitoxantrone; Osteopontin; Paclitaxel; r-Fluorouracil; Rituximab; Taxol; Thiotepa; Trastuzumab; Vinblastine; Vincristine; Vinorelbine.

Introduction

Chemotherapy is a systemic drug treatment in which chemotherapeutic drugs imparted to the blood circulate through all parts of the body for the purpose of controlling or killing the cancer. Most such drugs can be delivered through multiple pathways either directly into cancerous masses or injected (intravenously, into a muscle, under the skin, or into spaces around body tissues), administered intranasally or even swallowed (pill). However, not all drugs are available in all delivery forms [1-4]. I am here interested in those nano particles and delivery nano devices that have enabled NCT to emerge as an anti-cancer modality.

It is initially essential to be able to detect the presence of specific types of cancer and, after treatment, to assess the treatment efficacy. This is accomplished through tumor markers, the more common of which have been listed in (Table 1). Cancer detection is subsequently followed by treatment utilizing one or a combination of multiple drugs. Table 2 summarizes some of the more than 50 different chemotherapeutic drugs within six broad categories. Note that some cancers can be treated with drugs of different categories either singly or in combination (see last column of the Table) [4].

Table1: List of the more common tumor markers.

Antigens	Others
Carcinoembryonic	Human chorionic gonadotropic
Carbohydrate	Alpha-fetoprotein
Prostate-specific	5-Hydroxy indole acetic acid
	Serum paraproteins
	Nucleic acids

Table2: Broad classification of the different chemotherapeutic drugs.

Drug Category	Drug Names	Aim (S)	Cancer Types
Antibodies ("magic bullets")	<i>Bevacizumab, Cetuximab, Erlotinib*, Gefitinib*, Imatinib*, Rituximab*, Trastuzumab*</i> * also used in biological therapy that helps the immune system destroy the cancer cells	Cancer cells, sparing normal cells	Breast, colon, lung, lymphoma, several types of leukemia
Alkylating agents	<i>Busulfan, Carboplatin, Chlorambucil, Cisplatin, Curcumin, Cyclophosphamide, Thiotepa</i>	Cell's DNA (to prevent further cell division)	Chronic leukemia, non-Hodgkin's lymphoma, Hodgkin disease, multiple myeloma, lung, breast, ovary
Nitrosoureas	<i>Carmustine, Lomustine</i>	Interfere with enzymes that help repair DNA	Glioblastoma, non-Hodgkin lymphoma, multiple myeloma, melanoma
Antimetabolites	<i>Capeticabine, Cytarabine, Fludarabine, r-Fluorouracil, Gemcitabine, Methotrexate</i>	Alter enzyme functions in cell metabolism and protein synthesis, starving the cells to death	Leukemia (acute, chronic), breast, ovary, gastrointestinal tract
Antitumor antibiotics	<i>Dactinomycin, Daunorubicin, Doxorubicin, Epirubicin, Idarubicin, Mitoxantrone</i>	Bind with DNA and prevent RNA synthesis (imperative for cell survival)	Many different cancers
Miotic inhibitors	<i>Docetaxel, Paclitaxel, Vinblastine, Vincristine, Vinorelbine</i>	Inhibit cell division/ reproduction and use of certain proteins required for mitosis	Leukemia, lymphomas, lung, breast

What is Nano chemotherapy?

Nano chemotherapy (NCT) uses nano devices to deliver nano particles (NPs) containing cytotoxic drugs to tumors.

The basic process involves at least three steps:

- a. Anchoring or encapsulation of the drugs.
- b. Successful delivery of said drugs to the targeted region of the body
- c. Release of those drugs there.

This is followed by the assessment of the treatment efficacy [5]. The process is detailed below for various nano particle carriers.

Nano particle carriers

Several methods are employed whereby the cytotoxic drugs are either anchored to specially designed NPs or encapsulated within such particles. Thus:

Gelatin nano particles for delivering multiple drugs to the brain

Gelatin is biocompatible, biodegradable, and generally recognized as safe by the FDA. Gelatin nano particles are laced with the drug *osteopontin* (OPN). They can be administered intranasally along the olfactory nerve cells - a noninvasive and direct route to the brain, to reduce inflammation and prevent brain cell death. This delivery pathway bypasses the blood brain barrier (BBB) a biological fence that prevents the vast majority of drugs from entering the brain through the bloodstream. It can be most effective in delivering drugs that cannot otherwise cross it and it can deliver therapeutics agents to specific regions of the brain [6]. Once administered, the gelatin nano particles target damaged brain tissue thanks to an abundance of gelatin-munching enzymes produced in injured regions. As far as is known, gelatin particles have not yet been used clinically to treat glioblastomas.

Platelet-coated nano particles

The platelets (~100 nm in diameter) can deliver drugs to targeted sites in the body, particularly injured blood vessels, as well as organs infected by harmful bacteria. Delivered where needed, these NPs can greatly increase their therapeutic effects by directly depositing a much higher dose of medication specifically to diseased areas such as injured blood vessels and infected organs without saturating the entire body with drugs. This principle has broad implications for targeted therapy for other diseases than cancer such as neurological disorders.

Nutshells

These NPs (~120 nm in diameter) are coated with gold. They can be targeted to bond to cancerous cells by conjugated anti-bodies or peptides to the anopheles' surface. By irradiating the tumor with an infra-red (IR) laser, which passes through flesh without heating it, the gold is heated sufficiently to cause death to the cancer cells. It is to be noted that gold NPs strongly associate with essential blood proteins (albumin, fibrinogen, gamma-globulin, histone and insulin) and undergo conformational change upon association with the NPs [7].

Shape-shifting engineered nano particles

Nano particles can also be engineered to respond to biological molecules by changing shape to gain access to diseased tissue. These shape-shifters are made of minuscule chunks of metal with strands of DNA attached to them. This targeted molecular delivery system uses modular nano particles whose shape, size and chemistry can be altered by the presence of specific DNA sequences. The nano particles float around harmlessly in the blood stream until a DNA strand binds to a sequence of DNA known to be a marker for cancer (Table 1). When this happens, the particle changes shape then carries out its function: target the cancer cells, expose a drug molecule to the cancerous cell, and tag the cancerous cells with a signal molecule. This approach can theoretically be imbedded in personalized nano medical treatments, further tailoring the particles to deliver drugs to specified tumors and nowhere else.

Kinase inhibitors in nano particle formulation

Efforts to apply nanotechnology in cancer have focused almost exclusively on the delivery of cytotoxic drugs to improve therapeutic index. There has been little consideration of molecularly targeted agents, in particular kinase inhibitors, which can also present considerable therapeutic index limitations. Examples are accurin polymeric NPs that encapsulate the clinical candidate AZD2811 (an Aurora B kinase inhibitor) using an ion-pairing approach [8]. Accurins offer several advantages: increase bio-distribution to tumor sites, provide extended release of encapsulated drug payloads, show accumulation and retention in tumors with minimal impact on bone marrow pathology, and result in lower toxicity and increased efficacy. Accurins specifically, and nanotechnology in general, can increase the therapeutic index of molecularly targeted agents, including kinase inhibitors targeting cell cycle and

oncogenic signal transduction pathways. A phase-1 clinical trial is the next step for this novel nano medicine approach.

Bioavailability-improved nano scale particles and molecules

Nano scale particles and molecules can also be developed to improve drug bioavailability, i.e., the presence of drug molecules where they are needed in the body and where they will do the most good. Drug delivery focuses on maximizing bioavailability both at specific places in the body and over a period of time. It can be achieved by employing nano-engineered devices that target the molecules and deliver drugs with cell precision.

Nano delivery devices

Lipid-polymer and Polymeric hybrid nano particles: To overcome both the dose-limiting side effects of conventional chemotherapeutic agents and the therapeutic failure incurred from multidrug resistance (MDR), biodegradable lipid-coated polymeric hybrid nano particles (LPNs) and polymeric nano particles (PNPs) have been designed. These form a new generation of therapeutic delivery platforms for targeted and synergistic co-delivery of drugs. They are constituted of core-shell nano particle structures comprising polymer cores and lipid/lipid-PEG shells. The cores and the shells exhibit complementary characteristics of both polymeric nano particles and liposome's, particularly in terms of their physical stability and biocompatibility. They exhibit superior *in-vivo* cellular delivery efficacy compared to that obtained separately from polymeric nano particles and liposome's [8]. They can deliver a single drug or a combination of drugs. (They can also deliver genetic materials, vaccines, and diagnostic imaging agents.)

LPNs and PNPs loaded with multiple drugs have been used to treat several forms of cancer such as, for example:

- a. *Docetaxel* (DTX) and *Curcumin* (CUR): This combination is used to combat metastatic castration-resistant prostate cancer (mCRPC) patients. The synergism between these two drugs was also found to overcome multi-drug resistance [9].
- b. *Doxorubicin* (DOX) and CUR: Have been employed against osteosarcoma (OS) [10].
- c. *Cisplatin* (DDP) and CUR: Against cervix adenocarcinoma cell line (HeLa cells), the drug combination showed significantly higher *in-vitro* cytotoxicity and better *in vivo* antitumor activity than other formulations. LPNs were more efficacious than PNPs and free drugs [11].

Lipid-Based Surface Engineering of PLGA Nano particles: Poly (lactic-co-glycolic acid (PLGA)-based nano carriers are one of the most promising drug and gene delivery systems for crossing the BBB. While they offer great promise, they nevertheless present several major challenges, intrinsic drawbacks and require further engineering for clinical and research applications. These challenges include synthetic hydrophobic surface, low transfection efficiency, short circulation half-life, and nonspecific tissue distribution. To

overcome these problems, numerous engineering strategies have been employed with lipid-based surface functionalization of PLGA NPs showing promising results: enhancement of target specificity of the carrier, improvement of its physicochemical properties, NP-cell associations such as cellular membrane permeability, immune responses, and long in-vivo circulation half-life [12].

These challenges can be classified in three major categories:

- a. First generation NPs involving strategies to facilitate travel from the injection site.
- b. Second generation NPs involving BBB pre-transcytosis to enhance passage across the brain endothelial cells.
- c. Third generation NPs to achieve targeting of the impaired system cells (post-transcytosis strategies).

A fusion of all or some of these strategies may be required to engineer multi-functional PLGA NPs for treating neurological disorders for which pharmaceutical treatments have been limited due to drug access to the central nervous system (CNS) [13,14].

Engineered nano scale devices: Engineered nano scale devices (ENDs) are minute devices with the potential to be engineered to efficiently and more safely deliver drug treatments directly to the location of diseased cells while helping avoid harm to healthy cells that fall victim to toxic drugs administered by conventional means. Because of their diverse capabilities, nano scale devices can contain both targeting and therapeutic agents (in both single and multi-drug approaches). They can deliver high drug levels in several situations, including anticancer drugs at the tumor site that can increase chemotherapeutic efficacy. They can also offer the opportunity to develop new approaches to therapy, including “smart” nano therapeutics to “time” the release of any given drug or to deliver multiple drugs sequentially in a timed manner or at several locations in the body.

Hybrid nano crystals: A library has been developed of 800 different and uniquely shaped hybrid nano crystals. They are formed from ordered atom clusters. They act as new tools or molecular tags enabling and aiding targeted drug delivery [15]. These new nano crystals are multifunctional and able to be multi-tasked to do different things simultaneously. Their fabrication can be precisely controlled to create different shapes and sizes, allowing the assessment of the drug impact along its propagation path within the body.

Clinical advantages: Nano particles offer several clinical advantages, including:

- a. They circulate throughout the bloodstream without being attacked by the immune system.
- b. They preferentially bind to damaged blood vessels and certain pathogens such as Methicillin Resistant *Staphylococcus Aureus* (MRSA) bacteria, allowing them to deliver and release their drug payloads specifically to these body sites.

- c. They are non-toxic as the platelet membranes are nano particle cores made of a biodegradable polymer that can be safely metabolized by the body.

- d. They can be packed with many small drug molecules that diffuse out of the polymer core and through the platelet membrane onto their targets.

- e. They can overcome multi-drug resistance particularly after the failure of conventional chemotherapy and radiotherapy (see below).

Overcoming multi-drug resistance: Failure of conventional chemotherapy and radiotherapy is often accompanied by multi-drug resistance (MDR), which compounds the complexity and diversity of this deadly disease. Apart from typical physiological abnormalities and aberrant blood flow behavior, MDR cancers display several distinctive features such as higher apoptotic threshold, aerobic glycolysis, regions of hypoxia, and elevated activity of drug-efflux transporters. Additionally, MDR transporters play a pivotal role in protecting the cancer stem cells (CSCs) from chemotherapy and perhaps also in reviving tumors. Special NPs integrating a combination of all or part of the following (drugs, genes, imaging agents, targeting ligands) and using unique delivery platforms could be more efficient in treating MDR cancers [16].

Potential toxic effects: Notwithstanding their clinical advantages, nano materials may present potential toxic effects. Carbon nano materials [carbon fullerenes and carbon Nano tubes (CNT)] have been more extensively investigated because of their various applications in biomedical nanotechnologies, including drug delivery Nano systems. Thus, the use of CNTs in drug delivery systems has raised safety concerns, which led the FDA to undertake a research program onto the potential toxic effects of engineered nano particles and biologic micro particles in blood and their biomarker applications [17]. The investigation involved the outer membranes of blood cells, blood platelets isolated from blood, vessel wall cells grown in tissue cultures, and the cell membrane micro particles (MP) they release in the circulating blood. It was focused on blood and vascular biocompatibility of carbon nano materials.

Differential response to the same cancer treatment: Tracking the path of chemotherapeutic drugs in real time and at the cellular level could revolutionize cancer care and help sort out why two patients might respond differently to the same treatment. Up until now, this was accomplished, admittedly in a limited way, by organic dyes (that faded quickly) and by toxic elements (particularly, metals). Recently, researchers at the Ohio State University have devised an organic technique using nanotechnology to light up a common cancer drug *doxorubicin* (Table 2) or any other cancer drug. They could see where the chemotherapeutic drug goes and how long it takes to get there. They first created a luminescent molecule (a peptide made of two amino acids) and hitched it to the cancer medication so that it revealed the drug pathway and arrival within the cells [8]. Importantly, as it enters the cancerous

site, that peptide easily coexists with human cells and leaves them harmless as it is composed of natural amino acids. Further, the NP is inherently biocompatible.

Conclusion

Nano chemotherapy is emerging as an important anti-cancer modality supplementing traditional chemotherapy. It uses nano devices to deliver nano particles containing cytotoxic drugs to tumors in a three-pronged process (anchoring or encapsulation of the drugs; successful delivery of said drugs to the targeted region of the body; and release of those drugs). Of the nano particles discussed, gelatin laced with the drug *osteopontin* is biocompatible, biodegradable, and generally recognized as safe by the FDA. They can be administered most effectively intranasally along the olfactory nerve cells thereby bypassing the protective brain barriers. These advantages should be explored and applied clinically to the treatment of glioblastomas. Platelet-coated nano particles can deliver drugs to targeted sites (e.g., injured blood vessels, infected organs). Their therapeutic effects can be increased by directly depositing a much higher dose of medication specifically to diseased areas without saturating the entire body with drugs. Engineered nano particles can respond to biological molecules by changing shape to gain access to diseased tissue. This approach should be imbedded in personalized nano medical treatments, further tailoring the particles to deliver drugs to specified tumors and nowhere else.

While efforts to apply nanotechnology in cancer have focused almost exclusively on the delivery of cytotoxic drugs to improve therapeutic index, little consideration has been given to molecularly targeted agents (e.g., *accurin* encapsulating AZD2811 - an Aurora B kinase inhibitor). The multiple advantages of *accurin* (increased bio-distribution to tumor sites, extended release of encapsulated drug payloads, accumulation and retention in tumors with minimal impact on bone marrow pathology, lower toxicity and increased efficacy) represent a novel nano medicine approach that should be explored within clinical trials. Biodegradable lipid-coated polymeric hybrid nano particles and polymeric nano particles can overcome both the dose-limiting side effects of conventional chemotherapeutic agents and the therapeutic failure incurred from multidrug resistance. This new generation of therapeutic delivery platforms should be further developed for targeted and synergistic co-delivery of drugs and also genetic materials, vaccines, and diagnostic imaging agents.

Lipid-based surface engineering of poly (lactic-co-glycolic acid (PLGA)-based nano carriers are one of the most promising drug and gene delivery systems for crossing the blood brain barrier. Notwithstanding their challenges and drawbacks, their further engineering should be geared at clinical and research applications particularly for treating neurological disorders for which pharmaceutical treatments have been limited due to drug access to the central nervous system. Engineered nano scale devices offer the opportunity to develop new approaches to therapy, including "smart" nano therapeutics to "time" the release of any given drug

or to deliver multiple drugs sequentially in a timed manner or at several locations in the body. Notwithstanding their clinical advantages, nano materials may present potential toxic effects. Such effects deserve further investigations but should also involve the outer membranes of blood cells, blood platelets isolated from blood, vessel wall cells grown in tissue cultures, and the cell membrane micro particles they release in the circulating blood.

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