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Nanomedicine as a Precursor to Precision Medicine for Glioblastoma Treatment

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Abstract

Glioblastoma is the most common primary brain tumor in adults that remains an unmet need in Oncology. Delivery of therapeutic drugs is hampered by the presence of the blood brain barrier. Additional treatment difficulties are represented by the great heterogeneity of brain tumor cells, which limits the treatment efficacy and explains the high rate of progression of the disease. The standard treatment (surgery with maximal resection, followed by radio chemotherapy with the drug Temozolomide, followed by an adjuvant treatment with the same drug is of limited efficacy because the tumors often recur. However, treatment with nanotechnology may provide additional relief if not remission, I review here the various therapeutic nanotechnology strategies utilizing both nanoparticle carriers and nanodevices to deliver such particles. Included among nanoparticle carriers are: gelatins, platelet-coated nanoparticles, nutshells, shape-shifting engineered nanoparticles; kinase inhibitors and others. Included among delivery nanodevices are: lipid polymeric hybrid nanocarriers, Poly lactic-co-glycolic acid -based nanocarriers; engineered nanoscale devices, and hybrid nanocrystals. I also describe most recent research into a multiplexed nanomedicine platform against brain tumor-initiating cells. These latter cells are the key driver behind the therapy resistance, unstoppable malignant growth, and progression and recurrence of diffuse gliomas, particularly glioblastomas. They are elusive and exceptionally difficult to target not only because they reside across the BBB but also because of heterogeneous genetic and epigenetic aberrations that are challenging to reverse therapeutically using conventional pharmaceuticals or biologics. Combating them, however, offers a passage through the blood brain barrier. The clinical advantages of nanotechnology are highlighted as well as their potential toxic effects. Nanotechnology may also help explain multidrug resistance and why different patients respond differently to the same treatment. Some future research directions are outlined.

Keywords: *Blood Brain Barrier; Brain Tumor-Initiating Cells; Cancer Stem Cells; Chemoradiotherapy; Gelatin Nanoparticles; Glioma; Glioblastoma; Hybrid Nanocrystals; Kinase Inhibitors; Lipid Polymeric Hybrid Nanoparticles; Liposomes; Multi-Drug Resistance; Nanochemotherapy; Nanodevices; Nanomaterials; Nanooncology; Nanoparticles; Nanotechnology; Platelet-Coated Nanoparticles; Nutshells; Shape-Shifting Engineered Nanoparticles; Surgery; Temozolomide; Toxicity*

Abbreviations: BBB: Blood Brain Barrier; BTIC: Brain Tumor-Initiating Cells; CNS: Central Nervous System; CNT: Carbon Nano Tubes; CSC: Cancer Stem Cells; CUR: Curcumin; DDP: Cisplatin; DNA: DeoxyriboNucleic Acid; DOX: Doxorubicin; DTX: Docetaxel; END: Engineered Nanoscale Devices; FDA: (U.S.) Food and Drug Administration; GB: Glioblastoma; GBM: Glioblastoma Multiform; GY: Grey (a unit of measure of electromagnetic radiation dose); IR: Infra-Red; LPHNP: Lipid Polymeric Hybrid Nanoparticles; MDR: Multi-Drug Resistance; MP:

Micro Particles; MRSA: Methycillin Resistant Staphylococcus Aureus; NCT: NanoChemoTherapy; ND: NanoDevices; NM: NanoMaterials; NP: NanoParticles; NT: NanoTechnology; OPN: Osteopontin; PLGA: Polylactic-co-glycolic acid; PNP: Polymeric Nano Particles; RNA: RiboNucleic Acid; siRNA: Small-Interfering RNA; TMZ: Temozolomide.

Disorders mentioned: Cancer; Glioblastoma; Methycillin Resistant *Staphylococcus Aureus*; Neurologic Disorders; Osteosarcoma.

Drugs listed: Accurin; Cisplatin; Curcumin; Docetaxel; Doxorubicin; Osteopontin; Temozolomide

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INTRODUCTION

Glioblastoma (GB), also known as glioblastoma multiform (GBM) is the most common primary brain tumor in adults. It remains an unmet need in Oncology. Particulars of this disease are: Annual incidence – approximately 3.19 cases per 100,000 population; average age at diagnosis – 64 years; survival rate – about 1 year; 5-year survival: 5% of the people affected; no current cure at present. Although first-line treatment has been clearly defined since 2005, no standard second-line treatment has yet been determined. No prevention strategy is known even though several possible risk factors have been discussed. Most treatments cannot eradicate all tumor cells (surgery is often insufficient given the diffuse nature of the disease; chemotherapy has major limitations because most drugs cannot cross the blood–brain barrier (BBB), and penetration into brain cells is limited). In addition, the cells in brain tumors are greatly heterogeneous, which limits the treatment efficacy and explains the high rate of progression of the disease. The standard treatment consists of: (a) surgery (maximal resection) followed by (b) radiochemotherapy (6 weeks of radiotherapy at a dose of 60 Grey [Gy] together with concomitant chemotherapy with Temozolomide (TMZ) at a rate of 75 mg/m^2 daily); and once chemo radiotherapy is complete (c) adjuvant treatment (a minimum of 6 months with TMZ is started at a dose of 150–200 mg/m^2 for 5 days every 28 days). Even after treatment of primary and secondary tumors and their metastases, GB very often recurs.

Recent articles [1-4] have provided a comprehensive review of surgical and non-surgical management and treatment of GBs for primary and secondary tumors and their metastases in both cases of monotherapies or combination therapies, and for recurring tumors after treatment. For each such therapy, the treatment results obtained in clinical trials and other reported practices were also analyzed. At the outset, however, it must be recalled that chemotherapy (i.e., the use of one or a combination of selected cytotoxic drugs) has historically provided little durable benefit. Under such treatment, tumor recurs within several months even in the case of more accessible tumors located outside the brain. For brain tumors, the access is even more difficult because of the presence of the BBB. More effective therapies involving other options are required either in isolation or more likely in combination. Of these other options, the following were considered at some length: surgery, conformal radiotherapy, boron neutron therapy, intensity modulated proton beam therapy, antiangiogenic therapy, alternating electric field therapy...without neglecting palliative therapies. Research conducted in these and other options was also reviewed to include microRNA, immunotherapy, adjuvant therapy, gene therapy, stem cell therapy, and intranasal drug delivery. To these treatments, recent research has now added the use of nanotechnology (NT), which is the gist of this article.

Previous Nanotechnology Treatments

A series of recent articles has explored the capabilities of NT to penetrate the brain protective barriers to deliver therapeutic drugs to a variety of brain tumors including GB at the right location, at the right time, and in the right dose regimen [5-7].

Through the ability of nanoparticles (NP) imbedding therapeutic drugs and the nanodevices (ND) that deliver these drugs more efficiently and more judiciously at tumor sites, nanochemotherapy (NCT) is evolving as an emergent, viable anti-cancer modality that builds upon and supplements conventional chemotherapy. It uses NDs to deliver 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; and (c) Release of those drugs there. This is followed by assessment of the treatment efficacy.

NANODELIVERY CARRIERS

Several methods are employed whereby the cytotoxic drugs are either anchored to specially designed NPs or encapsulated within such particles. While at different stages of development in the case of cancers, in general, the following carriers have not, as far as is known, been applied to the delivery of single or multiple drugs to the brain. They are nonetheless described below to stimulate perhaps novel and creative ways of using them against GBs:

Gelatin nanoparticles

Gelatin is biocompatible, biodegradable, and generally recognized as safe by the U.S. Food and Drug Administration (FDA). Gelatin nanoparticles are laced with the drug *Osteopontin* (OPN). They can be administered intranasally along the olfactory nerve cells – a non-invasive and direct route to the brain, to reduce inflammation and prevent brain cell death. This delivery pathway bypasses the 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. Once administered, the gelatin nanoparticles target damaged brain tissue thanks to an abundance of gelatin-munching enzymes produced in the injured regions.

Platelet-coated nanoparticles

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, they 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 antibodies 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.

Shape-shifting engineered nanoparticles

NPs 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 NPs whose shape, size and chemistry can be altered by the presence of specific DNA sequences. The NPs float around harmlessly in the blood stream until a DNA strand binds to a sequence of DNA known to be a marker for cancer. 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 medical treatments, further tailoring the particles to deliver drugs to specified tumors and nowhere else.

Kinase inhibitors in nanoparticle formulation

Efforts to apply NT 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. *Accurins* offer several advantages: increase biodistribution 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 NT in general, can increase the therapeutic index of molecularly targeted agents, including kinase inhibitors targeting cell cycle and oncogenic signal transduction pathways.

Bioavailability-improved nanoscale particles and molecules

Nanoscale 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.

NANODELIVERY DEVICES

Lipid polymeric hybrid nanoparticles

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 NPs (LPHNP) and polymeric NPs (PNP) 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 nanoparticle structures comprising polymer cores and lipid/lipid-PEG shells. The cores and the shells exhibit complementary characteristics of both polymeric NPs and liposomes, particularly in terms of their physical stability and biocompatibility. They exhibit superior *in vivo* cellular delivery efficacy compared to that obtained separately from PNPs and liposomes. They can deliver a single drug or a combination of drugs. (They can also deliver genetic materials, vaccines, and diagnostic imaging agents.)

LPHNPs and PNPs loaded with multiple drugs have been used to treat several forms of cancer such as, for example: (a) Metastatic castration-resistant prostate cancer patients with *Docetaxel* (DTX) and *Curcumin* (CUR): The synergism between these two drugs was also found to overcome multiple drug resistance (MDR); (b) Osteosarcoma with *Doxorubicin* (DOX) and CUR; (c) Cervix adenocarcinoma with *Cisplatin* (DDP) and CUR: In this latter instance, using the cell line (HeLa cells), the drug combination showed significantly higher in vitro cytoxicity and better *in vivo* antitumor activity than other formulations. LPNs were more efficacious than PNPs and free drugs.

Lipid-Based Surface Engineering of PLGA Nanoparticles

Poly lactic coglycolic acid (PLGA)-based nanocarriers 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 and 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. 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; and (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).

Engineered nanoscale devices

Engineered nanoscale devices (END) 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, nanoscale 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" nanotherapeutics 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 nanocrystals

A library has been developed of 800 different and uniquely shaped hybrid nanocrystals. They are formed from ordered atom clusters. They act as new tools or molecular tags enabling and aiding targeted drug delivery. These new nanocrystals 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.

A NOVEL MULTIPLEXED NANOMEDICINE PLATFORM AGAINST BRAIN TUMOR-INITIATING CELLS

Brain tumor-initiating cells (BTIC) have been identified as the key driver behind the therapy resistance, unstoppable malignant growth, and progression and recurrence of diffuse gliomas, particularly GBs [8]. Previous research was aimed at either crossing or bypassing the BBB for the purpose of delivering therapeutic drugs behind the BBB [9,10]. Here, the difficulty of traversing the BBB is addressed head-on. The approach is to target the BTICs. These are elusive and exceptionally difficult to target not only because they reside across the BBB but also because of heterogeneous genetic and epigenetic aberrations that are challenging to reverse therapeutically using conventional pharmaceuticals or biologics. This situation highlights the urgent need to develop novel therapeutic strategies. Additionally, intra-tumoral heterogeneity and adaptations to therapeutic pressure by BTICs impede the discovery of effective anti-BTIC therapies and limit the efficacy of individual gene targeting.

Yua., *et al.* [8] have recently reported on the use of a LPHNP formulation (see in an earlier section a description of this technology) against glioblastoma, which is particularly difficult to treat because its genetic makeup varies from patient to patient. This new therapeutic approach would make it possible to target multiple cancer-causing gene products simultaneously in a particular patient's tumor. In this study, the scientists tested siRNAs that target four transcription factors highly expressed in many glioblastoma tissues -- but not all. The therapy worked against classes of glioblastoma BTICs with high levels of those transcription factors, while other classes of the cancer did not respond. Using mouse models of brain tumors implanted with BTICs derived from human patients, the scientists injected nanoparticles containing small interfering RNA (siRNA) -- short sequences of RNA molecules that reduce the expression of specific cancer promoting proteins -- directly into the tumor. In this new study, the strategy stopped tumor growth and extended survival when the therapy was administered continuously through an implanted drug infusion pump. It demonstrated two important features: (a) a surprisingly high affinity for BTICs and [2] the capacity to encapsulate multiple siRNA for potent and targeted anti-BTIC therapy. It has also shown, at least in mouse experiments, that direct infusion of LPHNP siRNAs to brain tumors effectively impedes tumor growth and provides encouraging survival benefits. This multiplexed nanomedicine platform carries strong potential for personalized anti-BTIC therapies. It also establishes a flexible nonviral gene therapy platform with the capacity to address the challenges posed by tumor heterogeneity. It paints a picture for personalized glioblastoma therapy regimens based on tumor profiling. Customized nanomedicine could target the unique genetic signatures in any specific patient and potentially lead to greater therapeutic benefits.

OVERCOMING MULTI-DRUG RESISTANCE

Failure of conventional chemotherapy and radiotherapy is often accompanied by 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 (CSC) 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.

The above strategy could also apply to other medical conditions related to the CNS system – not just brain tumors. such as degenerative neurological diseases or even psychiatric conditions.

CLINICAL ADVANTAGES

NPs offer several clinical advantages, including:

1. They circulate throughout the bloodstream without being attacked by the immune system;
2. They preferentially bind to damaged blood vessels and certain pathogens such as Methycillin Resistant *Staphylococcus Aureus* (MRSA) bacteria, allowing them to deliver and release their drug payloads specifically to these body sites;
3. They are non-toxic as the platelet membranes are NP cores made of a biodegradable polymer that can be safely metabolized by the body;
4. They can be packed with many small drug molecules that diffuse out of the polymer core and through the platelet membrane onto their targets; and
5. They can overcome MDR particularly after the failure of conventional chemotherapy and radiotherapy.

POTENTIAL TOXIC EFFECTS

Like for any anti-cancer modality, toxic effects may be lurking in the background. This is also the case for nanomaterials (NM), which may present potential toxic effects. Carbon NMs [carbon fullerenes and carbon nanotubes (CNT)] have been more extensively investigated because of their various applications in biomedical nanotechnologies, including drug delivery nanosystems. 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 NPs and biologic microparticles in blood and their biomarker applications. 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 microparticles (MP) they release in the circulating blood. It was focused on blood and vascular biocompatibility of carbon NMs.

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 the common cancer drug *Doxoribucin* 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. 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 NPs are inherently biocompatible.

CONCLUSIONS AND FUTURE DIRECTIONS

Nanochemotherapy is emerging as an important anti-cancer modality supplementing traditional chemotherapy. It uses nanodevices to deliver nanoparticles containing one or more 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 several nanoparticles discussed, gelatin capsules laced with the drug *osteopontin* are biocompatible, biodegradable, and generally recognized as safe. 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. Another promising approach would consist in employing a novel multiplexed nanomedicine platform targeting directly brain tumor-initiating cells, which are the key driver behind the therapy resistance, unstoppable malignant growth, and progression and recurrence of diffuse gliomas, particularly GBs. This is an additional strategy for creating a passage through the blood brain barrier to reach glioblastomas.

Biodegradable lipid-coated polymeric hybrid nanoparticles and polymeric nanopaticles 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 polylactic-co-glycolic acid (PLGA)-based nanocarriers 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 nanoscale devices offer the opportunity to develop new approaches to therapy, including "smart" nanotherapeutics 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, nanomaterials 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 microparticles they release in the circulating blood.

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