Nanoparticles and CNS Delivery of Therapeutic Agents in the Treatment of Primary Brain Tumors

Gerardo Caruso*, Daniele Marino and Maria Caffo

Neurosurgical Clinic, Department of Neuroscience, University of Messina School of Medicine, Messina, Italy

Abstract: Patients affected by malignant brain tumor present an extremely poor prognosis, notwithstanding improvements in surgery techniques and therapeutic protocols. Late diagnosis and the limitation of conventional therapies are major reasons for this unsolved clinical problem. The blood-brain barrier formed by a complex of endothelial cells, astrocyte and pericytes reduces notably the diffusion of a large number of therapeutic agents.

Nanotechnology involves the design, synthesis, and characterization of materials and devices that have a functional organization in at least one dimension on the nanometer scale. The nanoparticles have emerged as potential vectors for brain delivery able to overcome the difficulties of modern strategies. Nanoparticles drug delivery systems can be, also, used to provide targeted delivery of drugs, improve bioavailability, sustains release of drugs for systemic delivery. Moreover, multi-functionality can be engineered into a single nanoplatform so that it can provide tumor-specific detection, treatment, and follow-up monitoring.

In this study we will focus on the blood-brain barrier role and possibilities of its therapeutic overcoming. Recent studies of some kinds of nanoparticles systems in brain tumors treatment are summarized.

Keywords: Blood-Brain Barrier, Brain Tumors, Glioma, Glioblastoma Multiforme, Nanoparticles.

INTRODUCTION

In the United States the incidence rate for primary brain and nervous system tumors is 20.6 cases per 100,000; one-third of these lesions are malignant [1]. Metastatic brain tumors are the most common intracranial neoplasm in adults, and although the exact incidence is unknown, it has been estimated that they can occur in up to 30% of patients [2]. Classically, brain tumors are based on consequence of abnormal growth of a specific cell type [3]. Gliomas are the most common primary brain tumors in adults with a worldwide incidence of approximately 7 out of 100,000 individuals per year [4]. The WHO classification further divided glial tumors evaluating the principal cell type and the degree of anaplasia [3].

Surgery is the standard treatment for brain tumors; the objective is to preserve and improve the quality of life and prolong the survival of the patient. However, in patients affected by glioblastoma multiforme (GBM), despite recent advances in traditional therapeutic approaches, including the gamma knife and chemotherapy with temozolamide, the average survival is around 15 months [5-7]. Radiation therapy and chemotherapy are non-invasive options used as adjuvant therapy, but may also be effective for treating early phases of the disease. However, radiotherapy gives limited benefits and causes side effects. The value of systemic chemotherapy is limited by the blood-brain barrier (BBB) that limits the passage of a large number of therapeutic compounds and by toxic effects on healthy cells [8-11].

Nanoparticles (NPs) are able to increase transport across the BBB and for this reason can be adopted in the treatment of brain tumors. NPs are microstructural materials with a length scale less than 100nm. Since their first advent in the 1970s, NPs have been notably developed and applied to several fields, including biomedicine [12]. The sub-micron size of nanoparticle systems confers considerable advantages, including targeted delivery, higher- and deeper tissue penetrability, and greater cellular uptake [13]. NPs can be engineered to be multifunctional showing the ability to target diseased tissue, carry imaging agents for detection, and deliver multiple therapeutic agents for combination therapy. By encapsulating drugs inside a nanocarrier the solubility and stability of the drugs can be improved [4]. Chemotherapy-loaded NPs have resulted in sustained release formulations that can lower systemic toxicity and produce greater antitumor effects.

In this study we will focus on the brain drug delivery and on the potential efficacy of the nanoparticles drug delivery systems in brain tumors treatment.

BRAIN DRUG DELIVERY

The BBB is a functional structure that limits the transport of molecules between the blood and the

*Address correspondence to this author at the Neurosurgical Clinic, Department of Neurosciences, A.O.U. Policlinico "G. Martino", via Consolare Valeria, 1, 98125 Messina, Italy; Tel: ++39-090-2217167; Fax: ++39-090-693714; E-mail: gcaruso@unime.it

ISSN: 1927-7210 / E-ISSN: 1927-7229/14

brain. BBB function is to maintain a constant environment inside the brain and to protect the brain against toxic substances [5]. Key components of the BBB include the tight junctions between endothelial cells, the pericytes in the basement membrane, and the astrocyte endfoot processes. The BBB is highly permeable to water, CO_2, oxygen and lipid-soluble substances like alcohol, while it is slightly permeable to electrolytes, and almost completely impermeable to plasma proteins and many organic molecules. In addition the presence of efflux pumps, multidrug resistance proteins and the exposure of degrading enzymes in further decrease the efficacy of many chemotherapeutic drugs [14].

Physiological approaches to cross the BBB evaluated the capacity of specific substances such as glucose, insulin, growth hormones and low-density lipoproteins to interact with specific receptors in order to penetrate the BBB [14]. These approaches are favoured by the necessity of the brain for essential nutrients, by the brain's high perfusion rate and by reduced distances that separate its capillaries. The receptor-mediated transcytosis is characterized by targeting selected receptors at the BBB by specific ligands, modified ligands, and antibodies. Therapeutic compounds cross the BBB after conjugation to these specific ligands. Adsorptive-mediated endocytosis is characterized by an electrostatic interaction between a positively charged substance and the negatively charged sites on the brain endothelial cell surface [15]. This approach permits the passage of various peptides such as albumin, dextran, ferritin, IgG.

The intranasal delivery is a non-invasive method of bypassing the BBB delivering the substances to the nasal epithelium. The highly permeable nasal epithelium allows rapid drug absorption to the brain due to high total blood flow, porous endothelial membrane, and large surface area [16]. Nevertheless intranasal delivery can damage the nasal mucosa when frequently used and the drug can be rapidly cleared by the mucociliary system [17].

The temporary disruption of the BBB represents another strategy for the cross of the BBB. Hypertonic solutions can open the tight junctions thanks to their higher osmotic pressure, which leads to a shrinking of cerebrovascular endothelial cells and subsequent disarrangement of extracellular proteins [16, 18]. This technique is currently used clinically for delivering of chemotherapy to the CNS in patients with brain tumors. Biologically vasoactive agents such as bradykinin, angiotensin peptides, leukotrienes, and histamine are also capable to disrupt the BBB. Intracerebral delivery involves intrathecal or intraventricular catheters strategies or controlled release matrices. These techniques are highly invasive and related to important disadvantages such as infections, catheter obstruction, and limited volume of drug distribution. Micro-particles can be easily implanted stereotaxically in precise areas of the brain without damaging the surrounding tissue. Local delivery of chemotherapeutic agent's increases drug concentration at the tumor target, decreases systemic exposure and toxicities, and increases the duration of exposure of the tumor to the drug.

Prodrugs are pharmacologically inactive compounds that result from transient chemical modifications of biologically active species. The chemical change improves some deficient physicochemical property, such as membrane permeability or water solubility. After administration, the prodrug is converted to the active form, usually *via* a single activating step. Once in the CNS, hydrolysis of the modifying group will release the active compound. While increased lipophilicity may improve movement across the BBB, it also tends to increase uptake into other tissues, causing an increased tissue burden. Moreover, while increased lipophilicity may facilitate drug uptake into the CNS, it also enhances efflux processes. This can result in poor tissue retention and reduced biological efficacy.

Genetic engineering is used to produce either chimeric or humanized forms of monoclonal antibodies (MAbs) [19]. The most potent antibody-based molecular Trojan horse known to date is the one against the human insulin receptor [20]. Recently, this antibody has been humanized, and shown to cross the BBB *in vivo* in non-human primates [19]. Certain peptidomimetic monoclonal antibodies act as ligands for the receptor mediated transport (RMT) systems present on the BBB. These RMT-specific antibodies bind epitopes on the receptor which are spatially removed from the endogenous ligand binding site. The peptidomimetic MAbs act as Trojan horses to ferry across the barrier drugs, proteins, antisense agents, or non-viral plasmid DNA.

Convection-enhanced drug delivery (CED) consists in a local microinfusion of drug targeted directly to brain tissue. The basics consist in a continuous infusion pressure gradient to result in distribution of the drugs into the interstitial space. The CED technique is used primarily for large molecular weight agents that show

minimal leakage across the BBB and/or have significant systemic toxicity, including viruses, oligonucleotides, nanoparticles, liposome, and targeted immunotoxins [21]. Parameters that affect CED volume of distribution include infusion parameters (rate, volume, duration, cannula size), infusate characteristics (molecular weight, surface properties), and tissue properties (tissue density, extracellular space, vascularity, and interstitial fluid pressure) [22]. Mechanisms for CED treatment failure include distribution inhomogeneity, high interstitial fluid pressure, and rapid efflux of agent from the injection site.

NANOPARTICLES DRUG DELIVERY SYSTEMS AND APPLICATION IN BRAIN TUMORS

NPs drug delivery systems have been produced with the principal aim to improve the biodistribution and therapeutic index of therapeutic compounds. Drugs can be absorbed onto the surface, encapsulated, or dissolved within the matrix of these vehicles. The use of NP systems implies a reduced dose of drug and a selective drug delivery to target tumor cells. The process occurs both into the tumoral core and in the distal areas of the lesion, also characterized from integrity of the BBB [10]. This evenience is crucial in early diagnosis, in recurrences, in preoperative histological and grade diagnosis, and in preoperative treatment planning. However, the primary consideration when designing any drug delivery system is to achieve more effective therapies, by controlling the drug concentration in the therapeutic window, reducing cytotoxic effects, and improving patient compliance. By using nanotechnology in drug design and delivery, it will be also possible to deliver the drug to the targeted tissue, to release the drug at the controlled rate, and to escape from degradation processes. In brain tumor treatment, various molecules implicated in different pathways, such as apoptosis escape, tumor neoangiogenesis, and invasion have been studied as possible targets of novel therapeutic models. The possibility to block more contemporary pathway into tumor by molecular-based targeted approaches represents an interesting therapeutic strategy to deliver drugs and/or genetic probes into neoplastic cells [5, 12].

Nanoparticles like polymers, micelles, liposomes, graphene are efficiency drugs delivery systems.

Polymeric Nanoparticles

Polymeric NPs are arranged of different natural or synthetic biodegradable polymers. Polymeric NPs are formulated using emulsion/solvent evaporation or solvent displacement techniques. Using these methods, a variety of therapeutic agents including both low molecular weight drugs and high molecular weight DNA or antisense oligonucleotides can be encapsulated [23]. Polymeric NPs are structured in two different forms, nanospheres and nanocapsules. In nanospheres, the drug is dispersed in a polymeric matrix, whereas in nanocapsules, the drug is contained in a hydrophobic core surrounded by a polymeric membrane [24]. These carriers show a higher stability in biological fluids and against the enzymatic metabolism. The core matrix of these NPs can be composed by various biodegradable polymers, such as poly(lactic-coglycolic acid) PLGA, chitosan, poly (alkylcyanoacrylate) PACA, poly(butylcyanoacrylate) PBCA, poly(lysine), poly(ε-caprolactone), and PAsp (polyaspartate). Polymeric NPs have been used as transport vectors for various substances after intravenous injection such as hexapeptide dalargin, loperamide, tubocurarine and doxorubicin [25]. Paclitaxel is a potent anticancer agent less useful for clinical administration due to its poor solubility. This drug, encapsulated in PLGA intermingled with vitamin E, and tocopheryl polyethylene glycol succinate (TPGS) has shown good activity and much faster administration in comparison to traditional formulation [26]. More, poly(ethyleneglycol)-co-poly(e-caprolactone) (PEGePCL) NPs were conjugated to Angiopep and structured with paclitaxel. The administration of this compound in U87 MG glioma cells evidenced a higher cell uptake and stronger inhibition and apoptosis toward glioma cells due to LRP-mediated endocytosis [27]. The evaluation of the complex ketoprofen-loaded biodegradable polymer nanocapsules (Keto-NC), in various glioma cell lines, has demonstrated decreased cell viability, and a reduction *in vivo* of glioma growth. Further, the authors observed not evidenced toxicity to astrocytes [28]. In another study, a polymeric NP vector was structured with iron oxide, for MR imaging, and temozolomide (TMZ) [29]. The observations showed a clear reduction of the growth of glioma xenografts and an extension of the survival of animals. In a recent study, the plasmid encoding proapoptotic Apo2 ligand/tumor necrosis factor-related apoptosis-inducing ligand (Apo2L/TRAIL) was structured with cationic albumin-pegylated NP. The intravenous injection of this complex into the host cell genome caused inhibition of tumor growth and an extended survival [30].

Micelles

Micelles are amphiphilic spherical structures composed of a hydrophobic core and a hydrophilic

shell. The hydrophilic shell stabilizes the micelle in an aqueous environment for intravenous delivery and the hydrophobic core stores a payload of drug for therapy [31-32]. Micelles are highly biocompatible and show a remarkable flexibility in terms of design modification. This can allow the incorporation of a range of drug release mechanisms and targeting moieties into their structure [33]. Micelles can be engineered by means of ligand coupling or addition of pH-sensitive moieties according to the biological characteristics of the diseased site for active targeting. Micelles are internalized into the cells *via* fluid-state endocytosis. The lesion may be targeted with micelles by exploiting the enhanced permeability and retention (EPR) effect, by making micelles of stimuli responsive amphiphilic block copolymers, or by attaching specific targeting ligand molecules to the micelle surface [34]. The tumor vasculature features such as leaky endothelial cells, increased vascular tortuosity, abnormal basement membrane, increased the permeability of the tumoral vessels. Thus, numerous studies have shown that the EPR effect causes passive accumulation of macromolecules and NPs in solid tumor, enhancing the therapeutic index while decreasing side effects.

17-Allylamino-17-demethoxy geldanamycin (17-AAG) is an inhibitor of heat shock protein 90 (HSP90), a member of chaperone proteins that regulate various phases of cellular proliferation and survival. However, 17-AAG shows poor water solubility, a short biological half-life and evident hepatotoxicity limiting its clinical use. In a recent study, the authors structured polymeric micelles composed of Pluronic ®P-123 incorporating 17-AAG [35]. The authors evidenced, in U87MG human GBM cells, a 5-fold increase in the cytotoxicity of 17-AAG-loaded micelles. A polyion complex micelle was conjugated with an RGD-containing pentapeptide, ie, c(RGDfC, Cyclo(-Arg-Gly-Asp-D-Phe-Cys), forming an encapsulated poly-(aspartic acid) ion complex, ie, the c(RGDfC) polyionic complex micelle. c(RGDfC) polyionic complex micelles selectively inhibited proliferation of glioma cells *in vitro* [36]. Zhan *et al*. designed the cyclic RGD peptide (cRGD) with PEG-PEI polymeric micelle for delivery of the gene for tumor necrosis factor-related apoptosis-inducing ligand (pORF-hTRAIL). In U87 mouse model, the authors demonstrated a increased survival in these animal models [37]. Jiang *et al*. studied the cRGD-modified poly(trimethylene carbonate)-based micelles coupled with paclitaxel in an intracranial U87MG mouse model. cRGD modification was found to enhance micellar penetration into U87MG glioma spheroids in culture as well as into intracranial tumors *in vivo* [38]. Recently a complex characterized by biodegradable poly(ethylene glycol)-polylactide (PEG-PLA) copolymeric micelles and biotin groups was structured. The compound was, successively bounded to transferring (Tf). The flow cytometer measurement demonstrated the targeting ability of the NPs to tumor cells *in vitro* [39]. More, mice treated with Tf-modified micelles containing paclitaxel showed significantly prolonged survival when compared to animals treated with Taxol [40]. Recently, a promising chemotherapeutic drug (SN-38) incorporated in micelles was compared with camptothecin (CPT)-11, for the treatment of GBM in mice. The results demonstrated that micelles coupled with SN-38 showed more relevant growth-inhibitory effects than those of CPT-11 [41].

Liposomes

Liposomes are vesicles made up of a lipid bilayer resembling a cell membrane. The liposome bilayer is mainly composed of phospholipids and cholesterol. Pharmacokinetics and bioavailability of liposome-based drugs depend on size, charge, membrane lipid packing, and steric stabilization, as well as on the administered dose and route of administration. After PEGylation modification, liposomes behave as a sterically stabilized one, due to enhanced hydrophilicity imparted by polymers' hydrophilic chains, a lower contact angle between particles and phagocytic cells of body, and due to the lesser interaction between serum opsonins, thereby preventing opsonisation [42]. Because of their characteristics, liposomes are attractive transport systems, especially for delivering drugs to the brain. Glioma cells show an increased expression of IL-13 receptor α2 on their surface cells. In a recent study, has been demonstrated the inhibition of the growth of subcutaneously implanted gliomas; in this experimental study, the authors have structured a liposome coupled with doxorubicin and targeted with conjugated IL-13 [43]. PEGylated doxorubicin loaded liposomes can enhance delivery across the BBB after intravenous administration in rabbits. Doxorubicin was present in the brain only after administration of the NP formulation and the extent of doxorubicin transport was dependent on the extent of PEG modification [44]. The efficacy of the combination of temozolomide and pegylated liposomal doxorubicin (PLD) in pazients affected by GBM was also evaluated. The median time to progression was 6.2 months and overall survival was 13.4 months [45]. In a phase-I/II trial, the effects of pegylated liposomal doxorubicin (Caelyx™, PEG-Dox)

and prolonged administration of temozolomide in addition to radiotherapy were investigated in patients affected by GBM. The study confirmed the safety and feasibility of the approach, without however indicating improved treatment effects [46].

Graphene Nanoparticles

Graphene is an innovative two-dimensional nanomaterial possessing particular chemical configuration, unique physical, electronic, optical, thermal and mechanical characteristics [47-48]. It is a carbon allotrope with a bidimensional hexagonal structure and, together with its related derivatives, such as graphene oxide (GO), has shown great potentials in the biomedical research [49-50]. GO is a versatile material for various applications which range from targeting controlled drug/gene delivery, photothermal and photodynamic cancer therapy, biological sensing and imaging, to multifunctional nanoplatforms [51]. In oncology, GO nanoparticles (GONPs) have been studied for the treatment of different tumor types, both as native molecule and as drug delivery vehicle [51-53]. As an example, non-targeted GONPs were tested for the treatment of primary tumors given its enhanced permeability and retention effect [54]. Instead, other researches were conducted in targeted nanomaterials to detect, visualize, and destroy cancer cells with minimal side effects on normal cells [55].

One of the first attempts at using graphene for the treatment of gliomas employed its property as carrier. The chemotherapeutic drug 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU), widely used for the treatment of brain tumors, has poor thermal stability and a short half-life. Immobilization of BCNU on a nanocarrier might increase its stability and extend its half-life. GONPs were conjugated with polyacrylic acid (PAA) to improve the aqueous solubility and increase the cell penetration efficacy, and used as nanocarrier for BCNU. This nanocarrier significantly prolonged the half-life of bound BCNU and showed efficient intracellular uptake by GL261 cancer cells [56]. The photothermal activity of graphene has also been investigated in the treatment of brain tumors. The mechanisms of graphene-mediated photothermal killing of cancer cells apparently involved oxidative stress and mitochondrial membrane depolarization resulting in mixed apoptotic and necrotic cell death characterized by caspase activation/DNA fragmentation and cell membrane damage, respectively. Despite lower NIR-absorbing capacity, a suspension of polyvinylpyrrolidone-coated graphene sheets exposed to NIR radiation generated more heat than carbon nanotubes under the same conditions. Subsequently, graphene nanoparticles performed significantly better in inducing photothermal death of U251 human glioma cells *in vitro* [57]. A more recent study combined the chemo-photothermal targeted therapy of gliomas within one novel multifunctional drug delivery system using a targeting peptide (IP)-modified mesoporous silica-coated graphene nanosheet (GSPI). Doxorubicin (DOX) was conjugated with the GSPI-based system (GSPID), showing synergistic chemo-photothermal properties. Cytotoxicity experiments demonstrated a highest rate of death of glioma cells compared to that of single chemotherapy or photothermal therapy. Furthermore, the IP modification could significantly enhance the accumulation of GSPID within glioma cells. Exposure to graphene induced apoptosis in both glioma cell lines but with different results: 68% in U87 and 99% in U118 cells [58].

CONCLUSIONS

Nanotechnology is the developed of functional systems at molecular scale obtained through the finely controlled manipulation of matter on atomic, molecular, and supramolecular scale. Nanotechnology has been developing rapidly in the field of biomedicine and provides various choices in disease diagnosis and treatment.

The treatment of brain tumors remains nowadays a great challenge. Targeted therapies have been recently applied in different kinds of tumor, achieving also interesting results in some cases, but their efficacy remains low when practiced in brain tumor. The major biological challenge is to identify efficient targets on brain tumors. However, there are several factors underlying the disappointing results in brain cancer treatment including limited tumor cell drug uptake, intracellular drug metabolism, inherent tumor sensitivity to chemotherapy, cellular mechanisms of resistance, and poor delivery through the BBB.

Brain tumors and especially GBM show a complex biologic process characterized by various steps and numerous key molecules. For this reason, probably, a therapy acting on a single molecular mechanism results ineffective. A better knowledge of the genetic bases of gliomas and of the invasive behavior may suggest more molecular targets to overcome these limits [59]. New genomic approaches have allowed the subdivision of the brain tumors into molecular subtypes [60-61]. Emerging therapeutic targets are those broadly

referred to as members of the DNA damage response (DDR). There are now quite a few small molecule inhibitors targeting the DDR. These include inhibitors of poly-(ADP)-ribose polymerase (PARP), ataxia telangeictasia (A-T) mutated (ATM) kinase, A-T and RAD3-related (ATR) kinase, and the checkpoint kinases CHK1 and CHK2 [62-63]. More, others potential molecular targets are represented by the inhibitor of apoptosis family (IAP, c-IAP1, livin), by metalloproteinases, and by clusterin. Interleukin-8 that acts within HIF-1α pathway could represent another valid target [5, 64-65].

Nanotechnology provides a innovative opportunity of molecular treatment thanks to the engineering of nanomedicines specifically interacting with tumor cells and able to cross the BBB. Being tumor-specific targeted, nanodrugs will show more efficacies with fewer side effects because it is possible to use of a lower dose of drug with a selective delivery to target tumor cells. NPs are able to detect the tumor at an early-stage and act on cancer-specific markers. It is, also, possible to take selective contrast enhancement molecules to visualize brain tumors and to study *in vivo* all of their characteristics in a higher definition. Engineering of NPs for combined therapeutic and diagnostic applications (theranostic nanoparticles) requires that the surface of NPs can be modified to achieve targeted delivery and improved biocompatibility. Compounds may also be encapsulated within the interior core of NPs for multiple functions creating multifunctional nanoparticle platforms. Platforms are able to target multiple tumor markers and deliver multiple agents simultaneously, acting as diagnostic molecular imaging agents and carrying different type of drug at same time. For the in situ delivery of biological molecules, cell encapsulation provides a promising alternative, with the advantage of BBB circumvention, long term release of the active therapeutic molecule and reduced side effects. Although nano-derived applications have great potentials, there are some concerns about their adverse effects on human health and environment as suggested by nanotoxicology research. That because the properties that make NPs so promising can have an impact on the ecosystem, depending on the size, shape, and chemical composition of the particle. Nanotechnology is still a relatively young field, and little is known about the long-term effects of exposure to nanomaterials, especially in clearance organs such as the liver, spleen, and kidneys. Only a few data support the utilization of the materials constituting these nanotechnology based systems in view of drug transport across the BBB and delivery into the brain for human applications. Furthermore, the potential toxicity associated with the wide variety of nanomaterials available, ranges from completely inert to highly toxic. There is the need for further studies aimed at getting a basic understanding on how they interact with the biological system in terms of biocompatibility and biodistribution, and biosafety.

REFERENCES

[1] Kohler BA, Ward E, McCarthy BJ, Schymura MJ, Ries LA, *et al*. Annual report to the nation on the status of cancer, 1975-2007, featuring tumors of the brain and other nervous system. J Natl Cancer Inst 2011; 103: 714-36. http://dx.doi.org/10.1093/jnci/djr077

[2] Caffo M, Barresi V, Caruso G, Cutugno M, La Fata G, Venza M, *et al*. Innovative therapeutic strategies in the treatment of brain metastases. Int J Mol Sci 2013; 14: 2135-74. http://dx.doi.org/10.3390/ijms14012135

[3] Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, Burger PC, Jouvet A, *et al*. The 2007 WHO classification of tumours of the central nervous system. Acta Neuropathol 2007; 114: 97-109. http://dx.doi.org/10.1007/s00401-007-0243-4

[4] Caruso G, Caffo M, La Fata G, Passalacqua M, Merlo L, Tomasello F. Nanomedicine in brain tumors. In: Tiwari A, Tiwari A, editors. Bioengineered nanomaterials. 1st ed. Boca Raton: CRC Press 2013; p. 295-326. http://dx.doi.org/10.1201/b15403-14

[5] Caruso G, Caffo M, Raudino G, Alafaci C, Salpietro FM, Tomasello F. Antisense oligonucleotides as an innovative therapeutic strategy in the treatment of high-grade gliomas. Recent Pat CNS Drug Discov 2010; 5: 53-69. http://dx.doi.org/10.2174/157488910789753503

[6] Lima FR, Kahn SA, Soletti RC, Biasoli D, Alves T, da Fonseca AC, *et al*. Glioblastoma: therapeutic challenges, what lies ahead. Biochim Biophys Acta 2012; 1826: 338-49.

[7] Stupp R, Hegi ME, van den Bent MJ, Mason WP, Weller M, Mirimanoff RO, *et al*. Changing paradigms-an update on the multidisciplinary management of malignant glioma. Oncologist 2006; 11: 165-80. http://dx.doi.org/10.1634/theoncologist.11-2-165

[8] Caffo M, Raudino G, Caruso G. Nanotechnology and brain tumors drug delivery. Recent Patents Nanomed 2013; 3: 26-36. http://dx.doi.org/10.2174/1877912311303010005

[9] Ruben JD, Dally M, Bailey M, Smith R, Mclean CA, Fedele P. Cerebral radiation necrosis: incidence, outcomes, and risk factors with emphasis on radiation parameters and chemotherapy. Int J Radiat Oncol Biol Phys 2006; 65: 499-508. http://dx.doi.org/10.1016/j.ijrobp.2005.12.002

[10] Caruso G, Caffo M, Alafaci C, Raudino G, Cafarella D, Lucerna S, *et al*. Could nanoparticles systems have a role in the treatment of cerebral gliomas? Nanomedicine 2011; 7: 744-52. http://dx.doi.org/10.1016/j.nano.2011.02.008

[11] Meyers JD, Doane T, Burda C, Basilion JP. Nanoparticles for imaging and treating brain cancer. Nanomedicine 2013; 8: 123-43. http://dx.doi.org/10.2217/nnm.12.185

[12] Caruso G, Caffo M, Raudino G, Tomasello F. Nanoparticles and brain tumor treatment. 1st ed. New York: ASME Press; 2012. http://dx.doi.org/10.1115/1.860038

[13] Brigger I, Dubernet C, Couvreur P. Nanoparticles in cancer therapy and diagnosis. Adv Drug Deliv Rev 2002; 54: 631-51. http://dx.doi.org/10.1016/S0169-409X(02)00044-3

[14] Gabathuler R. Approaches to transport therapeutic drugs across the blood-brain barrier to treat brain diseases. Neurobiol Dis 2010; 37: 48-57. http://dx.doi.org/10.1016/j.nbd.2009.07.028

[15] Orringer D, Koo Y, Chen T, Kopelman R, Sagher O, Philbert M. Small solutions for big problems: the application of nanoparticles to brain tumor diagnosis and therapy. Clin Pharmacol Ther 2009; 85: 531-4. http://dx.doi.org/10.1038/clpt.2008.296

[16] Pardridge WM. Blood-brain barrier delivery. Drug Discov Today 2007; 12: 54-61. http://dx.doi.org/10.1016/j.drudis.2006.10.013

[17] Ali J, Ali M, Baboota S, Sahani JK, Ramassamy C, Bhavna DL. Potential of nanoparticulate drug delivery systems by intranasal administration. Curr Pharm Des 2010; 16: 1644-53. http://dx.doi.org/10.2174/138161210791164108

[18] Gelperina S, Maksimenko O, Khalansky A, Vanchugova L, Shipulo E, Abbasova K, *et al*. Drug delivery to the brain using surfactant-coated poly(lactide-co-glycolide) nanoparticles: influence of the formulation parameters. Eur J Pharm Biopharm 2010; 74: 157-63. http://dx.doi.org/10.1016/j.ejpb.2009.09.003

[19] Boado RJ, Zhang Y, Zhang Y, Pardridge WM. Humanization of anti-human insulin receptor antibody for drug targeting across the human blood-brain barrier. Biotechnol Bioeng 2007; 96: 381-91. http://dx.doi.org/10.1002/bit.21120

[20] Pardridge WM, Kang YS, Buciak JL, Yang J. Human insulin receptor monoclonal antibody undergoes high affinity binding to human brain capillaries *in vitro* and rapid transcytosis through the blood-brain barrier *in vivo* in the primate. Pharm Res 1995; 12: 807-16. http://dx.doi.org/10.1023/A:1016244500596

[21] Vogelbaum MA. Convection enhanced delivery for the treatment of malignant gliomas: symposium review. J Neurooncol 2005; 73: 57-69. http://dx.doi.org/10.1007/s11060-004-2243-8

[22] Raghavan R, Brady ML, Rodriguez-Ponce MI, Hartlep A, Pedain C, Sampson JH. Convection-enhanced delivery of therapeutics for brain disease, and its optimization. Neurosurg Focus 2006; 20: E12. http://dx.doi.org/10.3171/foc.2006.20.4.7

[23] Prabha S, Labhasetwar V. Critical determinants in PLGA/PLA nanoparticle mediated gene expression. Pharm Res 2004; 21: 354-64. http://dx.doi.org/10.1023/B:PHAM.0000016250.56402.99

[24] Lockman PR, Mumper RJ, Khan MA, Allen DD. Nanoparticle technology for drug delivery across the blood-brain barrier. Drug Dev Ind Pharm 2002; 28: 1-13. http://dx.doi.org/10.1081/DDC-120001481

[25] Misra A, Ganesh S, Shahiwala A, Shah SP. Drug delivery to the central nervous system: A review. J Pharm Pharm Sci 2003; 6: 252-73.

[26] Dritschilo A, Huang CH, Rudin CM, Marshall J, Collins B, Dul JL, *et al*. Phase I study of liposome-encapsulated c-raf antisense oligodeoxyribonucleotide infusion in combination with radiation therapy in patients with advanced malignancies. Clin Cancer Res 2006; 12: 1251-9. http://dx.doi.org/10.1158/1078-0432.CCR-05-1260

[27] Xin H, Jiang X, Gu J, Sha X, Chen L, Law K, *et al*. Angiopep-conjugated poly(ethylene glycol)-co-poly(e-caprolactone) nanoparticles as dual-targeting drug delivery system for brain glioma. Biomaterials 2011; 32: 4293-305. http://dx.doi.org/10.1016/j.biomaterials.2011.02.044

[28] da Silveira EF, Chassot JM, Teixeira FC, Azambuja JH, Debom G, Beira FT, *et al*. Ketoprofen-loaded polymeric nanocapsules selectively inhibit cancer cell growth *in vitro* and in preclinical model of glioblastoma multiforme. Invest New Drugs 2013; 31: 1424-35. http://dx.doi.org/10.1007/s10637-013-0016-y

[29] Bernal GM, La Riviere MJ, Mansour N, Pytel P, Cahill KE, Voce DJ, *et al*. Convection-enhanced delivery and *in vivo* imaging of polymeric nanoparticles for the treatment of malignant glioma. Nanomedicine 2014; 10: 149-57. http://dx.doi.org/10.1016/j.nano.2013.07.003

[30] Lu W, Sun Q, Wan J, She Z, Jiang X. Cationic albumin-conjugated pegylated Nanoparticles allow gene delivery into brain tumors *via* intravenous administration. Cancer Res 2006; 66: 11878-86. http://dx.doi.org/10.1158/0008-5472.CAN-06-2354

[31] Adams ML, Lavasanifar A, Kwon GS. Amphiphilic block copolymers for drug delivery. J Pharm Sci 2003; 92: 1343-55. http://dx.doi.org/10.1002/jps.10397

[32] Kataoka K, Harada A, Nagasaki Y. Block copolymer micelles for drug delivery: design, characterization and biological significance. Adv Drug Deliv Rev 2001; 47: 113-31. http://dx.doi.org/10.1016/S0169-409X(00)00124-1

[33] Morshed RA, Cheng Y, Auffinger B, Wegscheid ML, Lesniak MS. The potential of polymeric micelles in the context of glioblastoma therapy. Front Pharmacol 2013; 4: 1-14. http://dx.doi.org/10.3389/fphar.2013.00157

[34] Dabholkar RD, Sawant RM, Mongayt DA. Polyethylene glycol-phosphatidylethanolamine conjugate (PEG-PE)-based mixed micelles: some properties, loading with paclitaxel, and modulation of P-glycoprotein-mediated efflux. Int J Pharm 2006; 315: 148-57. http://dx.doi.org/10.1016/j.ijpharm.2006.02.018

[35] Saxena V, Hussain MD. Formulation and *in vitro* evaluation of 17-allyamino-17-demethoxygeldanamycin (17-AAG) loaded polymeric mixed micelles for glioblastoma multiforme. Colloids Surf B Biointerfaces 2013; 112: 350-5. http://dx.doi.org/10.1016/j.colsurfb.2013.07.031

[36] Liu X, Cui W, Li B, Hong Z. Targeted therapy for glioma using cyclic RGD-entrapped polyionic complex nanomicelles. Int J Nanomed 2012; 7: 2853-62. http://dx.doi.org/10.2147/IJN.S29788

[37] Zhan C, Meng Q, Li Q, Feng L, Zhu J, Lu W. Cyclic, R.G.D-polyethylene glycol-polyethylenimine for intracranial glioblastoma-targeted gene delivery. Chem Asian J 2012; 7: 91-6. http://dx.doi.org/10.1002/asia.201100570

[38] Jiang X, Sha X, Xin H, Xu X, Gu J, Xia W, *et al*. Integrin-facilitated transcytosis for enhanced penetration of advanced gliomas by poly(trimethylene carbonate)-based nanoparticles encapsulating paclitaxel. Biomaterials 2013; 34: 2969-79. http://dx.doi.org/10.1016/j.biomaterials.2012.12.049

[39] Ren WH, Chang J, Yan CH, Qian XM, Long LX, He B, *et al*. Development of transferrin functionalized poly(ethylene glycol)/poly(lactic acid) amphiphilic block copolymeric micelles as a potential delivery system targeting brain glioma. J Mater Sci Mater Med 2010; 21:2673-81. http://dx.doi.org/10.1007/s10856-010-4106-5

[40] Zhang P, Hu L, Yin Q, Zhang Z, Feng L, Li Y. Transferrin-conjugated polyphosphoester hybrid micelle loading paclitaxel for brain-targeting delivery: synthesis, preparation and *in vivo* evaluation. J Control Release 2012; 159: 429-34. http://dx.doi.org/10.1016/j.jconrel.2012.01.031

[41] Kuroda J, Kuratsu J, Yasunaga M. Potent antitumor effect of SN-38-incorporating polymeric micelle, NK012, against malignant glioma. Int J Cancer 2009; 124: 2505-11. http://dx.doi.org/10.1002/ijc.24171

[42] Kang JS, De Luca PP, Lee KC. Emerging PEGylated drugs. Expert Opin Emerg Drugs 2009; 14: 363-80. http://dx.doi.org/10.1517/14728210902907847

[43] Madhankumar AB, Slage-Webb B, Mintz A, Sheehan JM, Connor JR. Interleukin-13 receptor-targeted nanovesicles are a potential therapy for glioblastoma multiforme. Mol Cancer Ther 2006; 5: 3162-9. http://dx.doi.org/10.1158/1535-7163.MCT-06-0480

[44] Zara GP, Cavalli R, Bargoni A, Fundarò A, Vighetto D. Intravenous administration to rabbits of non-stealth and stealth doxorubicin-loaded solid lipid nanoparticles at increasing concentrations of stealth agent: pharmacokinetics and distribution of doxorubicin in brain and other tissues. J Drug Target 2002; 10: 327-35. http://dx.doi.org/10.1080/10611860290031868

[45] Ananda S, Nowak AK, Cher L, Dowling A, Brown C, Simes J, Rosenthal MA. Phase 2 trial of temozolomide and pegylated liposomal doxorubicin in the treatment of patients with glioblastoma multiforme following concurrent radiotherapy and chemotherapy. J Clin Neurosci 2011; 18: 1444-8. http://dx.doi.org/10.1016/j.jocn.2011.02.026

[46] Beier CP, Schmid C, Gorlia T, Kleinletzenberger C, Beier D, Grauer O, *et al*. RNOP-09: pegylated liposomal doxorubicine and prolonged temozolomide in addition to radiotherapy in newly diagnosed glioblastoma -a phase II study. BMC Cancer 2009; 9: 308. http://dx.doi.org/10.1186/1471-2407-9-308

[47] Rao CNR, Sood AK, Subrahmanyam KS, Govindaraj A. Graphene: The new two-dimensional nanomaterials. Angew Chem Int Ed 2009; 48: 7752-77. http://dx.doi.org/10.1002/anie.200901678

[48] Zhang K, Zhang LL, Zhao XS, Wu J. Graphene-polyaniline nanofiber composites as supercapacitor electrodes. Chem Mater 2010; 22: 1392-401. http://dx.doi.org/10.1021/cm902876u

[49] Fang F, Long J, Zhao WF, Wang L, Chen G. pH-Responsive chitosan-mediated graphene dispersions. Langmuir 2010; 26: 16771-4. http://dx.doi.org/10.1021/la102703b

[50] Sun ST, Wu PY. A one-step strategy for thermal- and pH-responsive graphene oxide interpenetrating polymer hydrogel networks. J Mater Chem 2011; 21: 4095-7. http://dx.doi.org/10.1039/c1jm10276a

[51] Yang K, Feng L, Shi X, Liu Z. Nano-graphene in biomedicine: theranostic applications. Chem Soc Rev 2013; 42: 530-47. http://dx.doi.org/10.1039/c2cs35342c

[52] Hu H, Yu J, Li Y, Zhao J, Dong H. Engineering of a novel pluronic F127/graphene nanohybrid for pH responsive drug delivery. J Biomed Mater Res A 2012; 100: 141-8. http://dx.doi.org/10.1002/jbm.a.33252

[53] Shen H, Zhang L, Liu M, Zhang Z. Biomedical applications of graphene. Theranostics 2012; 2: 283-94. http://dx.doi.org/10.7150/thno.3642

[54] Iyer AK, Khaled G, Fang J, Maeda H. Exploiting the enhanced permeability and retention effect for tumor targeting. Drug Discov Today 2006; 11: 812-8. http://dx.doi.org/10.1016/j.drudis.2006.07.005

[55] Sun X, Liu Z, Welsher K, Robinson JT, Goodwin A, Zaric S, Dai H. Nano-Graphene oxide for cellular imaging and drug delivery. Nano Res 2008; 1: 203-12. http://dx.doi.org/10.1007/s12274-008-8021-8

[56] Strakova N, Ehrmann J, Dzubak P, Bouchal J, Kolar Z. The synthetic ligand of peroxisome proliferator-activated receptor-gamma ciglitazone affects human glioblastoma cell lines. J Pharmacol Exp Ther 2004; 309: 1239-47. http://dx.doi.org/10.1124/jpet.103.063438

[57] Markovic ZM, Harhaji-Trajkovic LM, Todorovic-Markovic BM, Kepić DP, Arsikin KM, Jovanović SP, *et al*. *In vitro* comparison of the photothermal anticancer activity of graphene nanoparticles and carbon nanotubes. Biomaterials 2011; 32: 1121-9. http://dx.doi.org/10.1016/j.biomaterials.2010.10.030

[58] Stockmann-Juvala H, Naarala J, Loikkanen J, Vähäkangas K, Savolainen K. Fumonisin B1-induced apoptosis in neuroblastoma, glioblastoma and hypothalamic cell lines. Toxicology 2006; 225: 234-41. http://dx.doi.org/10.1016/j.tox.2006.06.006

[59] Caruso G, Raudino G, Caffo M. Patented nanomedicines for the treatment of brain tumors. Pharm Pat Analyst 2013; 2: 1-10. http://dx.doi.org/10.4155/ppa.13.56

[60] Kuan CT, Wakiya K, Herndon JE, Lipp ES, Pegram CN, Riggins GJ. MRP3; A molecular target for human glioblastoma multiforme immunotherapy. BMC Cancer 2010; 10: 1-15. http://dx.doi.org/10.1186/1471-2407-10-468

[61] Gerstner ER, Yip S, Wang DL, Louis DN, Iafrate AJ, Batchelor TT. MGMT methylation is a prognostic biomarker in elderly patients with newly diagnosed glioblastoma. Neurology 2009; 73: 1509-10. http://dx.doi.org/10.1212/WNL.0b013e3181bf9907

[62] Evers B, Helleday T, Jonkers J. Targeting homologous recombination repair defects in cancer. Trends Pharmacol Sci 2010; 31: 372-80. http://dx.doi.org/10.1016/j.tips.2010.06.001

[63] Bolderson E, Richard DJ, Zhou BB, Khanna KK. Recent advances in cancer therapy targeting proteins involved in DNA double-strand break repair. Clin Cancer Res 2009; 15: 6314-20. http://dx.doi.org/10.1158/1078-0432.CCR-09-0096

[64] Venza M, Visalli M, Alafaci C, Caffo M, Caruso G, Salpietro FM, *et al*. Interleukin-8 overexpression in astrocytomas is induced by prostaglandin E2 and is associated with the transcription factors CCAAT/enhancer-binding protein-Î² and CCAAT/enhancer-binding homologous protein. Neurosurgery 2011; 69: 713-21. http://dx.doi.org/10.1227/NEU.0b013e31821954c6

[65] Venza I, Visalli M, Fortunato C, Ruggeri M, Ratone S, Caffo M, *et al*. PGE2 induces interleukin-8 derepression in human astrocytoma through coordinated DNA demethylation and histone hyperacetylation. Epigenetics 2012; 7: 1315-30. http://dx.doi.org/10.4161/epi.22446

Received on 13-03-2014 Accepted on 24-04-2014 Published on 30-04-2014

http://dx.doi.org/10.6000/1927-7229.2014.03.02.5