NANO-CARRIERS: AN EMERGING TREND FOR BRAIN TUMOR TREATMENT. A FRONTIER LOOK

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ABSTRACT

In current scenario, Brain tumors constitute an unsolved clinical problem although significant strides have been made in the treatment of many other cancer types. The incidence of primary brain tumors in the United States has been estimated at approximately 43,800 per year and 18,500 of these are expected to be malignant. Currently brain tumors account for at least 12,690 deaths in the United States yearly. Therapy of brain tumor still remains a challenge despite of recent improvements in surgery and multi adjuvant therapy. Drug therapies of brain tumor have been particularly inefficient, due to the blood-brain barrier and the non-specificity of the potentially toxic drugs. The nano-arriers has emerged as a potential vector for brain delivery, diagnosis & able to overcome the problems of current strategies. Moreover, multi-functionality can be engineered into a single platform so that it can provide tumor specific detection, treatment, and follow-up monitoring. Such multitasking is not possible with conventional technologies. The recent advances in nano-carrier based detection and treatment of brain tumor. The advantages of nano-carriers based delivery and the types of nano-carrier systems under investigation are described, as well as their applications. A broad spectrum of biocompatible nanoparticles, either synthesized or purified from the living body, has been investigated so far. The types of nanoparticles include polymeric, ceramic and metallic matrixes, polymeric micelles, liposomes and dendrimers. For cancer imaging, various types of nanoparticles have been investigated for MRI, optical imaging and ultrasound imaging. Several nanoparticle formulations have been clinically approved for MRI.

KEYNOTES: *MRI, Brain delivery, Nanoparticles, Brain cancer, Blood-brain barrier.*

1. INTRODUCTORY NOTES

Brain tumors have proved itself an unsolved clinical problem although significant strides have been made in the treatment of many other cancer types. The case of primary brain tumors in the US has been estimated at approximately 43,800/year and 18,500 of these are expected to be malignant. Currently brain tumors account for at least 12,690 deaths in the US yearly and are the most common cause of cancer-related death for children 0-14 years of age. The earliest stages of intracranial cancer remain difficult to detect and treat. This problem is confounded by the location of several brain tumors that lie adjacent to or within anatomical structures critical for basic motor, cognitive, reflexive and other functions. As with most other tumors, early detection and remediation correlates with a positive prognosis.[1] Currently an invasive biopsy is the preferred method to confirm the diagnosis of cancer as it can provide information about histological type, classification, grade, potential aggressiveness and other information that may help determine the best treatment. Modern imaging techniques such as CT, PET, ultrasound and MRI are rapidly emerging as standards in the detection of tumors and cancers. These imaging scans of malignant human brain tumors, however, do not readily allow quantization of the actual tumor volume since a lot of extracellular water (edema) can build up around the tumor site, making exact discrimination of tumor margins difficult. Moreover, the delivery of contrast agents is inefficient, due to the blood brain barrier (BBB).[2] The BBB is a very specialized system of endothelial cells that separates the blood from the underlying brain cells, providing protection to brain cells and preserving brain homeostasis. The use of contrast agents often allows estimates of tumor domains from the largest cross-sectional area of contrast enhancement, indicating a compromised BBB.[3] However, the contrast agents tend to diffuse away from the vessel, making precise measurements of the location of the disrupted BBB somewhat displaced. Finally, even in a tumor surrounded by an extensive zone of edema, there are most likely regions of infiltrating tumor cells which are not apparent. Therefore imaging is typically used to locate and stage neoplasm and visualize a tumor before biopsy or at the time of surgery.[4] The current practice of waiting for altered neurological function, neurological exam and pathological/ microscopic evaluation/confirmation of the malignancy usually requires that the tumor (benign or malignant) develops either a significant mass or potential for migration in the neuraxis before invasive surgical or non-invasive neuro-radiological therapies are invoked. Treatment of brain tumors, therefore, has historically consisted of surgery followed

by adjuvant therapy such as radiation therapy, chemotherapy and photodynamic therapy (PDT). Despite recent improvements in surgical and adjuvant therapy for brain tumors, the multimodality approach currently used in the treatment of malignant brain tumors does not produce a meaningful improvement in patient outcome.[5] Each treatment modality has limiting factors, as stated below. Surgery is invasive but currently the primary mode of treatment for the vast majority of brain tumors due to difficulties in finding a tumor at early stages.[6] One of the greatest challenges in brain tumor surgery is achieving a complete resection without damaging crucial structures near the tumor bed. Unfortunately, neoplastic tissue that is easily detected radiographically, is virtually indistin- guishable from normal brain. While surgery is the recommended initial treatment for brain tumors, it is rarely capable of eradicating all tumor cells.[7] Furthermore, surgery is not an option when eloquent structures are likely to be damaged during a resection. To address the inability of current surgical techniques to reliably eradicate residual or unresectable tumor, adjuvant radiation and chemotherapy regimens have been developed. Radiation therapy, chemotherapy and PDT are noninvasive and often used as adjuvant therapy after surgery but may also be effective for curing early-stage tumors. Radiation therapy usually results in a delayed, but well-documented, decline in cognitive function in adults, in addition to posing the risk of secondary malignancy in the irradiated area.[8] In children, radiation therapy is known to interfere with brain development.[9] The efficiency of radiation therapy is often hindered by diffusely invasive characteristics of brain tumors as well as the emergence of radiation resistant populations. Most chemotherapeutic agents have a low therapeutic index. They are toxic and can affect not only cancer cells but also healthy cells, which leads to severe systemic side effects, generally resulting in morbidity or mortality in the patient. The chemotherapeutic treatment of brain cancer is further restricted due to the ability of the BBB to exclude a wide range of anticancer agents.[10] Another limiting factor is the development of multi-drug resistance (MDR) by the cancer cells. A combinational chemotherapy, i.e. the use of more than one drug, is a common practice in clinical oncology. However, cancer cells often develop resistance against a wide variety of chemotherapeutic drugs, due to the very effective drug efflux system P-glycoprotein or multi-drug resistance-associated protein (MDRP).[11] The P-glycoprotein is an ATP-dependent transporter responsible for the cellular extrusion of a number of drugs. It is expressed in many tissues, including the luminal membrane of the cerebral endothelium. The combination of chemotherapy and radiation therapy has been implemented with variable success in adult brain tumors.[12] But also carries significant treatment-related morbidity. Moreover, the improvements in outcome

demonstrated with the use of combination therapy are minimal: a prospective randomized controlled study on temozolomide, the most effective and best tolerated agent for treating gliomas, demonstrated an increase in the median two-year survival of only 2.5 months in patients with newly diagnosed glioblastoma receiving radiation and temozolomide, compared to those receiving radiation therapy alone.[13] PDT involves the delivery of photosensitizers (PS) such as Photofrin® to tumors, combined with local excitation by the appropriate wavelength of light, resulting in the production of singlet oxygen and other reactive oxygen species which initiate apoptosis and cytotoxicity in many types of tumors, with minimal systemic toxicity. PDT has emerged as a promising method for overcoming some of the problems inherent in classical cancer therapies.[14-17] It is more selective and less toxic than chemotherapy because the drug is not activated until the light is delivered. PDT was initially applied clinically to cutaneous and bladder malignancies that can easily be exposed to light. However, PDT is also an interesting approach for the treatment of malignant gliomas, as it offers a localized treatment approach. Several investigations have been made on the application of PDT for the treatment of brain tumors.[18-25] Recently it was reported that PDT of primary and recurrent gliomas resulted in an increase in patient median survival.[26] The efficacy of PDT for brain cancer is also limited by the BBB and MDR, just like chemotherapy, as it requires the delivery of the PS to the brain. The therapeutic efficacy of chemotherapy and PDT can be greatly improved by efficient delivery of the drugs to the specific tumor location. The recent molecularly- targeting approach allows the medical intervention to affect only cancer cells but not the normal cells, based on molecular recognition processes (ligand–receptor or antibody–antigene interaction).[27-31] This innovative approach is inherently different from classical modalities. It has the potential to improve the therapeutic efficacy or imaging contrast enhancement, by increasing the amount of therapeutic or contrast agents delivered to the specific site and to minimize toxicity, or imaging background signal, by reducing systemic exposure. The promise of the molecularly targeted approach in imaging is that one may be able to obtain dramatic contrast enhancement so as to detect the tumor at an earlier stage than possible by current methods, with sensitivity good enough to avoid an invasive biopsy. Since the specific molecular signature of one brain tumor may be different from that of another and cannot be differentiated based upon traditional anatomical imaging, the ability to diagnose brain tumors based on their genetic presentation, in a targeted manner, would be of great value. By the same notion, the approach of delivering a therapeutic agent in a targeted manner should give clinicians the ability to treat cancer or to manage it as a chronic disease, thus preventing it from progressing to its

later, more virulent stages. Towards more efficient chemotherapeutic treatment of brain cancer, there have been continuous efforts to develop special delivery methods designed to overcome the BBB. Proper combination of these methods and the molecular-targeting approach should be a key factor for achieving an improved therapeutic efficacy.

2. OBJECTIVE OF THE STUDY

The major focus of this review article is-

- ➢ To gain all the background information about the Neurodegenerative disorders, etiology and novel treatments feasible especially on glioblastoma or brain cancer.
- ➢ To update the novel techniques and advancements in the field of nano-drug delivery system.
- ➢ To collect information regarding the drugs used in the treatment of above said disorder.
- ➢ To review the combination therapy of drugs (if any available) for the best possible results.
- ➢ To gain all the background information about the drug delivery to the central nervous system through the nano carrier system.
- ➢ To acquire the knowledge regarding the nano-carrier drug delivery system, the advantages and disadvantages, the types and the techniques involved.
- ➢ To correlate between the nano-carriers drug delivery and other dosage system.
- ➢ To gain the knowledge regarding the MOA of the drug delivery to the CNS.
- ➢ To know about the latest technique and advancement in the flied of drug delivery system to the CNS.
- ➢ To know about the various drugs available for disorder of CNS in nano-carriers form.
- ➢ The study and work achieved so far regarding it i.e. prior art to nano drug delivery.

3. DRUG DELIVERY METHODS FOR THE BRAIN

In contrast to the open endothelium of the peripheral circulation, the tightly fused junctions of the cerebral capillary endothelium, the anatomic basis for the BBB, essentially form a continuous lipid layer that effectively restricts free diffusional movement of molecules into and out of the brain. Only small, electrically neutral, lipid-soluble molecules (molecular weight up to 500 Da) can penetrate the BBB by passive diffusion and most chemotherapeutic agents do not fall into this category. Therefore, delivery of drugs to the brain needs a special strategy to bypass the BBB and thus to achieve high intratumoricidal drug concentrations within the central nervous system (CNS). Various strategies have been explored for manipulating the BBB, as summarized below.

2.1. Chemical modification of a drug and prodrugs

Lipid solubility is a key factor in enhancing passive diffusion into the BBB. Chemical modification of the drug itself into a more lipophilic and neutral form as well as a prodrug approach have been investigated. The prodrug approach involves the administration of the drug in a form that is inactive or weakly active, but readily able to penetrate the BBB and then to be converted into the active form within the brain. Both approaches have pharmacokinetic difficulties, as lipidization may bring in undesirable pharmacokinetic effects, such as increased uptake by the reticuloendothelial system and increasing non-specific plasma protein binding when administered intravenously.[32] For example, several lipophilic variants of BCNU were clinically tried but have not shown improved clinical efficacy over BCNU.[33]

2.2. Temporary disruption of the BBB

The BBB can be permeabilized using either osmotic disruption by certain hyperosmolar agents, such as mannitol, or biochemical opening by bradykinin analogs such as RMP-7. This leads to a reversible opening of the tight junction, but is not specific enough to disallow CNS entry of toxins and unwanted molecules, thus potentially resulting in significant damage. The experimental studies have clearly shown an increased penetration of the drug into the brain parenchyma, but the clinical studies did not show improvement in the efficacy of the drug with concurrent use of these agents. Therefore, this has not translated into clinical efficacy.[34]

2.3. Local delivery into brain

This method has been achieved by direct infusion of a drug via a catheter or implantation of a gel wafer, a polymer matrix containing a drug. It is, however, a highly invasive procedure that requires neurosurgery and special equipment. To date, Gliadel® Wafer (BCNU-loaded biodegradable polymer) is the only wafer approved for clinical use in the US; it releases the chemotherapy drug directly into the brain as the polymer degrades over 2–3 weeks. Clinical trials have shown that Gliadel wafers can lengthen survival time and help control symptoms of high grade gliomas for longer times than surgery and radiotherapy alone.[35] To date this is the most efficient method of delivery of drugs into the brain.

2.4. Convection-enhanced delivery (CED)

While invasive it is currently an area of active investigation for drug delivery to the CNS. This method utilizes convection so as to supplement diffusion for the distribution of certain compounds and thus treat much larger volumes of brain than can be achieved by diffusion

alone. The convection results from a simple pressure gradient and is independent of molecular weight, resulting in greater pharmacokinetic advantages over systemic administration.[34] The CED delivery system is currently used in two clinical treatment trials for high grade gliomas.[36,37]

2.5. Carrier/receptor-mediated delivery

The CNS (or brain) has transport routes that overcome the BBB by other than passive diffusion, such as carrier/receptor-mediated influx or transcytosis[38], in order to receive essential polar metabolites such as glucose, amino acids and lipoprotein. These carriers/receptors can be used to deliver drugs to the CNS It requires the discovery and develpment of receptor specific ligands, which can be attached directly to the drug of interest or the drug delivery system, such as nanoparticle and liposome. This methodology has been receiving significant attention with the remarkable development of nanotechnology and non-invasiveness, compared to the other delivery methods listed above. The combination of nanoparticles and delivery methods is especially promising.

4. NANO-PARTICULATE DRUG DELIVERY SYSTEM.

The ability to deliver effective concentrations of contrast or therapeutic agents selectively to tumors is a key factor for the efficacy of cancer detection and therapy. The utilization of the nanoparticle as a potential vector for brain or other site-specific delivery has the following advantages, due to its excellent engineerability and non-toxicity:

1. The loading/releasing of active agents (drugs/contrast agents) can be controlled. The drugs are loaded into nanoparticles by encapsulation, adsorption or covalent linkage. The loaded amount is controllable by changing the size of the nanoparticles or the number of linkers inside and on the surface of the nanoparticles. Each nanoparticle can carry a large amount of molecular therapeutic and/or contrast agents. Release of the agents may occur by desorption, diffusion through the NP matrix, or polymer wall and/or NP erosion, which can all be controlled by the type of the nanoparticle's polymer matrix, i.e., having it become swollen or degradable in the tumor environment.

2. Specific molecular-targeting factors can be attached for localized binding to and/or uptake by the tumor cells, as well as for passage through the blood–brain barrier when appropriate. It should be noted that the selective delivery of nanoparticles to tumor is sometimes achieved due to the leaky tumor vasculature, which is known as the enhanced permeability and retention (EPR) effect.[39-42] This and tumor-specific targeting moieties on the surface turn the

nano particles into very efficient delivery vectors for tumors. Moreover, the use of targeted nanoparticles can achieve the delivery of large amounts of therapeutic or imaging agents per targeting biorecognition event, which is a major clinical advantage over simple immunotargeted drugs.

3. A hydrophilic coating can be given to the nanoparticle to provide reduced uptake by the RES, resulting in both increased delivery of the nanoparticles to tumor sites and reduced toxicity to other body tissues.

4. The nanoparticle matrix provides protection, for the active agents, from enzymatic or environmental degradation.

5. The nanoparticles can alleviate the problem posed by the MDR of cancer cells against many drugs; done by masking the drugs entrapped within the nanoparticles. This feature may enhance the delivery of drugs that are normally excluded from tumors.

6. The nanoparticles can reduce immunogenicity and side effects. The maximum tolerated dose of the drug or contrast agents can be increased as the nontoxic (biocompatible) polymer reduces the exposure to toxicity. The nanoparticles with enhanced surface properties (targeting and/or hydrophilic coating) may be able to deliver a high amount of drugs/contrast agents selectively to tumor sites and improve the efficacy of existing imaging and treatment of cancer in general. Success of the nanoparticle delivery systems for brain cancer, however, depends on the ability of the nanoparticles to get across the BBB and enter the brain. Some nanoparticles have been found to successfully cross the BBB. They are often nanoparticles coated with surfactant (for example, polysorbate) or covalently linked to peptides. The exact mechanism of nanoparticle transport into the brain is not fully understood, but most likely relies on receptor-mediated endocytosis, phagocytosis and/or passive leakage of nanoparticles across defects in the blood–brain barrier.[38,43] For example, polysorbate-coated nanoparticles are thought to mimic low-density lipoproteins (LDL), allowing them to be transported into the brain by the same endocytotic process as LDL undergoes at the BBB.[44,45] Nanoparticles conjugated with synthetic peptides may be transported across the BBB presumably by a mechanism similar to that of the opioid peptides.[46] The opioid peptides bind to specific receptors on the capillary walls, which help carry the nanoparticles into the brain.[47] However, the BBB may be partially disrupted and altered by the brain cancer and thus allow the nanoparticles to penetrate into the brain.[48] The brain cancer may enhance the BBB

permeability by increased pinocytosis.[49] Furthermore, the brain concentration of the BBB permeable drug (by passive diffusion) can be significantly enhanced due to a large concentration gradient at the BBB resulting from the enhanced plasma concentration of the drug and its long plasma half-life.[50] These considerations suggest that nanoparticles are the ideal candidates for delivering drug/contrast agents for the purpose of recognizing and treating brain cancer. Furthermore, nanoparticles can be designed as multi-functional nanoplatforms that carry multiple components, for example, (1) imaging agents and (2) drugs, as well as (3) targeting ligands and (4) "cloaking" agents that avoid interference with the immune system. The multi-functional nanoparticle concept provides a new paradigm for cancer diagnosis and treatment, which integrates the efforts for detection, treatment and follow-up monitoring of the tumor response, leading to decisions about the need for further treatment.[51,52] This concept has drawn much interest from the cancer research community and there have been investigations to develop and translate this innovative nanoparticle-based strategy into clinical practice for various kinds of cancer, including brain cancer.[53-60]

3.1. Nanoparticle platform(Nanoplatform)

A broad spectrum of biocompatible nanoparticles, either synthesized or purified from the living body, has been investigated so far.[53,61-71] The types of nanoparticles include polymeric, ceramic and metallic matrixes, polymeric micelles, liposomes and dendrimers.[72] For cancer imaging, various types of nanoparticles have been investigated for MRI, optical imaging and ultrasound imaging.[73] Several nanoparticle formulations have been clinically approved for MRI.[61] For cancer therapy, liposome-encapsulated formulations of doxorubicin were approved 10 years ago. Recently, a polymeric nanoparticle-based drug, albumin–paclitaxel was approved for breast cancer.[74] Nanoparticle-based therapeutic or imaging agents have not yet been approved specifically for brain cancer. However, various types of nanoparticles have been investigated for brain cancer. In order to make a successful delivery across the BBB, the nanoparticles may need to have several properties such as avoidance of the reticuloendothelial system (RES), long circulation time, being stable in plasma, etc.[87] Initially, delivering nanoparticles to reach the brain in appreciable quantity was unsuccessful. Failure of the nanoparticles to reach the CNS was due to the nanoparticle uptake by the RES. A primary strategy to overcome the RES uptake and prolong plasma circulation time is the coating of the nanoparticles with hydrophilic polymers or surfactants and the use of hydrophilic nanoparticles. It should be noted that the nanoparticles are either coated with dextran, polysorbate or polyethylene glycol (PEG) or made of a hydrophilic matrix or

hydrogel (polyacrylamide) which has a long plasma circulation time even without additional surface coating. The size of the particles is an important factor determining the efficacy of cancer detection and therapy. For several reasons, the bigger the particle, the better. The contrast enhancement and therapeutic action all improve with the cube of the radius, due to the increased loaded amount of the agents. Also, the target recognition improves with the particle's surface area, i.e. with the square of the radius. However, the RES uptake of the nanoparticles may also increase with size. Although the efficiency and kinetics of particle delivery varies from one model to another, nanoparticles of 10–100 nm are believed to provide the best option because they are too large to undergo renal elimination and too small to be recognized by phagocytes.[41,88,89] The use of the nanoparticles for imaging of brain cancer has been mostly limited to MRI, which is the current gold standard imaging method for brain cancer. MRI is useful in both basic research and clinical settings, due to its inherent depth of imaging, low toxicity/discomfort, relatively high resolution and its permitting good contrast between healthy and abnormal tissues. Two different nanoparticle-based therapeutic modalities have been investigated for brain cancer is Chemotherapy and PDT. Multi-functionality is a key advantage of the nanoparticle-based approach for the cancer-specific delivery of therapeutic or imaging agents. Targeted dual imagings (MRI and Near IR optical imaging)[65,81] and targeted multifunctional nanoparticles for imaging (MRI) and therapy (PDT)[55-58] have been investigated.

3.2. Nanoparticle synthesis and characterization

The nanoparticles of different matrices and sizes are prepared by various methods and drug loading can be accomplished by absorption, adsorption, encapsulation and covalent linkage.[90] Covalent linkage of hydrophilic polymer or targeting ligands to the nanoparticles is typically made by a simple coupling reaction between amine-functionalized nanoparticles and succinimidyl ester derivatives. The physicochemical properties of the nanoparticles affect their functional efficiency and therefore should be well-characterized to produce quality controlled nanoparticles for the functional tests. The size, surface charge, surface morphology, hydrophobicity and the amount of drug/contrast agents and targeting peptides may be important parts of the nanoparticle characterization. The size and morphology of the dried nanoparticles are commonly determined by SEM (Scanning Electron Microscopy) while the size and extent of aggregation of nanoparticles in aqueous solution are determined by light scattering (LS). The encapsulated amount of drug or imaging agents is determined by elemental, spectrophotometric or chromatographic analysis. For example, the

superparamagnetic iron oxide content can be obtained from the % of iron present in the sample. The amount of drug such as Photofrin® or doxorubicin can be obtained by measuring the absorbance of the prepared nanoparticle sample solution and comparing it with the calibration curve constructed from the mixture of free drug and blank nanoparticles of known concentrations. The surface charge is determined by measuring the zeta potential.

Table-1: Examples of nanoparticles investigated so far for brain cancer

Function	Nanoparticle matrix	Key components	Size (nm)	Refs.
Imaging (MRI)	Dextran coated iron oxide	Iron oxide	20-30	75-79
	Polyacrylamide	Iron oxide PEG	30–70	60
	Stearic acid	Iron oxide	160–230	80
Imaging (MRI+optical)	Dextran- or PEG-coated iron oxide	Iron oxide Cy5.5 Chlorotoxin peptide	15-32	65,81
Therapy (Chemotherapy)	Polysorbate-coated poly(butylcyanoacrylate)	Doxorubicin	250-270	44,45,82,83
	Stearic acid or stearic acid–PEG 2000	Doxorubicin	60-100	84,85
	Emulsifying wax	Paclitaxel	< 100	85
Therapy (PDT)+ imaging (MRI)	Polyacrylamide Photofrin®	Iron oxide F3-peptide	30-70	55,58

4. Magnetic nanoparticles for MRI.

MRI of the CNS is usually performed with shortlived gadolinium-based contrast agents, which gives rapid and transient imaging of brain and spinal permeability. Iron oxide nanoparticle-based MRI contrast agents also show excellent potential for imaging in the CNS. The iron oxide contrast agents are termed superparamagnetic iron oxide (SPIO) or ultrasmall superparamagnetic iron oxide (USPIO), depending on the size distribution of the nanoparticles. Two generic types of magnetic nanoparticles have been used: iron oxide core with a polymer coating and polymeric nanoparticles with incorporated iron oxide crystals. Some of the SPIO and USPIO are already clinically approved or on preclinical trial. For example, Endorem® is approved for liver and spleen disease detection and Sinerem® (or Combidex®), an USPIO, is in Phase III stage for the detection of metastatic disease in lymph nodes. There have been continuous efforts to improve the efficiency of the agents and extend their applications to the CNS.

4.1. Iron oxide core surface-coated with polymer Dextran-coated USPIO have been investigated by in vitro cellular studies and in vivo animal studies as well as human studies in order to evaluate their efficacy as MRI contrast agents in the brain. The USPIO typically

consist of a 5–6 nm iron oxide core surrounded by a dextran coating to give a hydrodynamic diameter of 20–30 nm with light scattering.[75,78] The *in-vitro* cellular uptake studies were done in various tumor cells and primary isolates of different organs with 125I-labeled or fluorescently labeled dextran-coated iron oxide nanoparticles.[75,78] The cellular uptake was found to be varying but ubiquitous in different tumor cells and was not saturable, suggesting that it is based on fluid-phase endocytosis rather than receptor-mediated endocytosis. The *in-vivo* animal studies were performed on rats bearing implanted 9L gliosarcoma or C6 glioma cells.[75,78] MR imaging was performed 14 days after tumor implantation. All animals were imaged before and 24 h after injection of dextran-coated iron oxide nanoparticles (19 mg/kg iron). All the images were obtained with a 1.5-T superconducting magnet. The total amount of the nanoparticles taken up by the glioma was sufficient to alter the MR signal intensity at tumors, compared to that at adjacent brain tissues, in both T1-weighted and T2-weighted images. An *in-vivo* biodistribution study with 125I-labeled dextran-coated iron oxide nanoparticles showed that 24h after intravenous administration, the majority of the agents was localized in the liver, spleen and lymph nodes, with 1.9%, 9.8% and 25.9% of injected dose per gram of each tissue, respectively. Accumulation in brain tumor was low (0.11% of injected dose per gram of tumoral tissue) but was 10-fold higher than brain tissue adjacent to the tumor. The pattern of intratumoral distribution of the iron oxide nanoparticles was also studied by *ex-vivo* studies using fluorescent microscopy and immunohistochemistry. The nanoparticles accumulated preferentially in the tumor periphery and heterogeneously throughout the remainder of the tumor. The heterogeneity was correlated with the presence of vessels within individual histologic sections. The feasibility study to extend the use of the dextran-coated USPIO to human brain tumors has been done with Sinerem®.[77,78,91] All tested brains, including both primary and metastatic brain tumors, showed readily detectable T1 signal enhancement. Unlike the pattern of enhancement with Gd chelate, which occurs immediately and decreases within hours, the contrast enhancement with the USPIO occurred gradually, with a peak at 24–48 h after iron administration. The margin with the USPIO remained sharp with time while that with the Gd chelate blurred with time due to diffusion.

5. CONCLUDATORY COMMENS

This review on the brain tumor aims to summarize what is currently known about quality of life in patients with both low-grade and high-grade tumors and suggest how we may use this knowledge to direct future research. To date, reports on quality of life have been primarily qualitative and focused on specific symptoms such as fatigue, sleep disorders and cognitive

dysfunction, as well as some symptom clusters. However, the increasing interest in exploring quality of life as a primary end point for cancer therapy has established a need for prospective, controlled studies to assess baseline and serial quality-of-life parameters in brain tumor patients in order to plan and evaluate appropriate and timely interventions for their symptoms. The use of nanotechnology for therapy has grown exponentially over the last two decades. By comparison, the growth of nanotechnology in the imaging and treatment of brain cancer has only begun but has already shown great promise. In this review, we have briefly provided the reader with an overview of targeted NP design (inorganic or organic synthesis, functionalization and loading of drug payloads), as well as the exciting frontier of theranostics.

6. ACKNOWLEDGEMENT

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