Advanced Drug Delivery Reviews 66 (2014) 42–57

Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

journal homepage: www.elsevier.com/locate/addr

Multifunctional nanoparticles for brain tumor imaging and therapy ☆

Yu Cheng, Ramin A. Morshed, Brenda Auffinger, Alex L. Tobias, Maciej S. Lesniak *

The Brain Tumor Center, The University of Chicago, Chicago, IL, USA

ARTICLE INFO

Article history:
Accepted 13 September 2013
Available online 20 September 2013

Keywords:
Brain tumor
Nanotechnology
Nanoparticles
Theranostics
Imaging
Diagnosis
Therapy
Drug delivery

ABSTRACT

Brain tumors are a diverse group of neoplasms that often carry a poor prognosis for patients. Despite tremendous efforts to develop diagnostic tools and therapeutic avenues, the treatment of brain tumors remains a formidable challenge in the field of neuro-oncology. Physiological barriers including the blood–brain barrier result in insufficient accumulation of therapeutic agents at the site of a tumor, preventing adequate destruction of malignant cells. Furthermore, there is a need for improvements in brain tumor imaging to allow for better characterization and delineation of tumors, visualization of malignant tissue during surgery, and tracking of response to chemotherapy and radiotherapy. Multifunctional nanoparticles offer the potential to improve upon many of these issues and may lead to breakthroughs in brain tumor management. In this review, we discuss the diagnostic and therapeutic applications of nanoparticles for brain tumors with an emphasis on innovative approaches in tumor targeting, tumor imaging, and therapeutic agent delivery. Clinically feasible nanoparticle administration strategies for brain tumor patients are also examined. Furthermore, we address the barriers towards clinical implementation of multifunctional nanoparticles in the context of brain tumor management.

Contents

☆ This review is part of the *Advanced Drug Delivery Reviews* theme issue on "Cancer Nanotechnology".

* Corresponding author at: The Brain Tumor Center, The University of Chicago, Pritzker School of Medicine, 5841 South Maryland Ave, M/C 3026, Chicago, IL 60637, USA. Tel.: +1 773 834 4757; fax: +1 773 834 2608.
E-mail address: mlesniak@surgery.bsd.uchicago.edu (M.S. Lesniak).

0169-409X/$ – see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.addr.2013.09.006

1. Introduction

With the rapid development of nanotechnology for biomedical applications, it is expected that newly developed particle systems can have a revolutionary impact on brain cancer diagnosis and therapy [1–10]. In general, nanotechnology involves the design, synthesis, and application of materials with at least one dimension in the size range of 1–100 nm [3]. Multifunctional nanoparticles containing optical, thermal, and magnetic properties are promising systems that offer new opportunities to overcome the limitations of current brain tumor management options in the clinic. In this review, we begin by introducing the prognostic and biologic features of brain tumors, followed by the major obstacles facing brain tumor management. We then highlight recent advances and clinical applications of nanoparticles in brain tumor therapeutics, focusing on (i) tumor imaging, (ii) treatment and (iii) the combination of both imaging and therapeutic functions (*i.e.* theranostics). Furthermore, strategies for nanoparticle administration and regulation issues surrounding nanoparticle translation to clinic are discussed. Lastly, the barriers towards clinical implementation of these nanoparticles are discussed in order to bring better insight into strategies for developing the most feasible systems for treating brain tumor patients.

2. Brain tumors

Brain tumors, referring to a heterogeneous group of primary and metastatic neoplasms in the central nervous system, are life-threatening diseases characterized by low survival rate [11]. The annual incidence of primary malignant brain tumors is approximately 24,000 cases [11,12]. Malignant gliomas are primary tumors that are derived from glial origin and account for approximately 70% of new primary brain cancer diagnosis [12,13]. Of these, glioblastoma multiforme (GBM), a grade IV astrocytoma according to the World Health Organization (WHO) classification, is the most common and aggressive form in nature [14]. Most patients with brain tumors eventually succumb to the disease despite aggressive treatment approaches. The median survival is only about three years for anaplastic astrocytomas and around 14.6 months for GBM patients [15,16]. Brain metastases are another important class of tumors in the central nervous system originating mainly from systemic cancers in the lung, breast and skin [17]. Metastatic brain tumors occur at a high frequency with an estimated incidence of 100,000–170,000 cases in the USA annually [18].

Today, a multimodality treatment approach including surgical resection, radiotherapy, and chemotherapy is the current standard of care for malignant brain tumor patients [16]. It has been demonstrated that aggressive resection of a brain tumor and postoperative radiation lead to a significant survival advantage [16,19]. Adjuvant chemotherapy can be administered at different time points as well [20,21]. Cytotoxic and cytostatic agents are the two major categories of chemotherapy used to treat brain tumors. The mechanism of these agents involves direct tumor cell death, anti-angiogenesis, pro-differentiation, growth factor pathway disruption, and inhibition of tumor invasion. Temozolomide, an imidazotetrazine derivative, is a first line systemic chemotherapy agent used for patients with brain tumors [22–24]. Unconventional therapies including immunotherapy, gene therapy, and photodynamic therapy (PDT) are potential adjuvant treatments for brain tumors and are under clinical trials. These additive therapies have broadened the spectrum of therapeutic agents for brain tumors to antibodies, genetic material, and photosensitizers.

Furthermore, advancements in anatomical and functional imaging techniques for brain tumors play a critical role in management as it allows for early detection, surgical planning, and follow-up evaluation [25–30]. Imaging techniques including magnetic resonance imaging (MRI), computed tomography (CT), and positron-emission tomography (PET) are the most common modalities for brain tumor diagnosis, characterization and intraoperative imaging [31–34]. Other techniques such as fluorescence imaging have been developed for intraoperative fluorescence-guided tumor resection [35,36]. These imaging modalities can help delineate the boundaries between neoplastic and normal tissue, helping doctors determine the most appropriate course of treatment.

3. Major obstacles in brain tumor treatment

Despite tremendous efforts to develop diagnostic tools and therapeutic avenues, the treatment of brain tumors remains a formidable challenge in the field of neuro-oncology. The major obstacles to the successful treatment of brain tumors include a) the structural complexity of the brain, b) the heterogeneous and invasive nature of many brain tumors, c) difficulty in identifying tumor margins and disseminated tumor burdens, d) insufficient accumulation of therapeutic agents at the site of a tumor, and e) acquired drug resistance to chemotherapy.

The brain, arguably the most complex system in the body, controls a multitude of functions including information processing, perception, motor control, arousal, homeostasis, motivation, as well as learning and memory. Due to the complexity of brain functions, the treatment of brain tumors requires both robust and highly selective elimination of all cancerous tissues including those that invade beyond the main tumor mass into the surrounding normal tissue. Highly skilled surgeons are presented with the difficult task of accurately identifying all the diseased tissue and resecting it from the brain while attempting to preserve surrounding normal, functional tissue. Even after extensive removal, brain tumors usually recur locally within centimeters of the resection margin [37].

Adjuvant treatments including chemotherapy for brain tumors only achieve modest clinical outcomes. The effectiveness of systemic delivery of therapeutic agents to brain tumors is hampered by several physiological barriers. Unlike other organs, the brain is protected by the blood–brain barrier (BBB) [38–40]. The BBB prevents the influx of harmful endogenous and exogenous molecules from the bloodstream but also becomes a major limiting factor for anti-brain tumor therapy. The BBB is composed of tight junctions between endothelial cells, pericytes, a basement membrane, as well as the feet of astrocytes [39]. Normal brain capillaries act as a continuous lipid layer and exhibit selective permeability based on molecular solubility and size. Deficiency of pinocytotic vesicles within the cerebral endothelial cells compromises cellular transcytosis and further contributes to the selectivity of the BBB [39]. Additionally, ATP-binding cassette transporters such as P-glycoprotein act as drug efflux transporters and their high expression limits substrate transportation across the BBB [41–44]. Only small lipophilic molecules, electro-neutral molecules, and nutrients under 400–600 Da in the blood can diffuse passively into the brain [38,45–47].

The second barrier that blocks the passage of systemically administered therapeutic agents is known as the blood–cerebrospinal fluid barrier (CSF) [1,39]. It is formed by tightly bound choroid epithelial cells, which regulate molecule penetration within the interstitial fluid of the brain parenchyma. This barrier prevents most macromolecules from passing into the CSF through the bloodstream. In addition, the intact