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Review article

Drug delivery challenges and future of chemotherapeutic nanomedicine for glioblastoma treatment

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ABSTRACT

Glioblastoma (GBM) is one of the most aggressive and deadliest central nervous system tumors, and the current standard treatment is surgery followed by radiotherapy with concurrent chemotherapy. Nevertheless, the survival period is notably low. Although ample research has been performed to develop an effective therapeutic strategy for treating GBM, the success of extending patients' survival period and quality of life is limited. This review focuses on the strategies developed to address the challenges associated with drug delivery in GBM, particularly nanomedicine. The first part describes major obstacles to the development of effective GBM treatment strategies. The second part focuses on the conventional chemotherapeutic nanomedicine strategies, their limitations and the novel and advanced strategies of nanomedicine, which could be promising for GBM treatment. We also highlighted the prominence of nanomedicine clinical translation. The near future looks bright following the beginning of clinical translation of nanochemotherapy for GBM.

1. Glioblastoma multiforme and current standard of care

Glioblastoma (GBM) is one of the most aggressive and common tumors occurring in the central nervous system. GBM includes all tumors that arise from the intrinsic glial cells of the brain and from its supportive tissue. Approximately 19 in 0.1 million individuals are diagnosed with central nervous system (CNS) tumors and primary brain tumors every year worldwide. Of these diagnosed patients, 17% have GBM [1,2]. Although the incidence rate of GBM is notably low, the terrifying fact is that the median survival of GBM patients is 12-15 months [3].

GBM aggressiveness and deadliness is characterized by a heterogeneous set of cells that are genetically unstable. Histopathological characteristics of GBM include proliferative endothelial cells, increased blood vessel diameter, thickened basement membranes and necrosis with pseudo palisading features. GBM is the most angiogenic brain tumor, as it shows the highest degree of endothelial cell hyperplasia and vascular proliferation [2]. GBM is not only highly heterogeneous but also very infiltrative and is surrounded by peritumoral edema and inflammation. GBM exhibits indistinct tumor margins and therefore cannot be completely resected [4]. Collectively, these unique characteristics of GBM provide a challenge for the current treatment options and ongoing research to cure GBM.

The current standard treatment for GBM includes surgical resection followed by adjuvant radiation and chemotherapy. Surgery involves an adequate balance to minimize morbidity while maximizing survival with quality of life [5]. In the majority of cases, surgery is performed because it relieves pressure (caused by the tumor in the brain) by debulking of the tumor. Depending on the accessibility and location of the tumor, surgery, e.g., standard craniotomy, biopsy or awake craniotomy, is performed. In newly diagnosed GBM, complete surgical resection primes better survival compared to biopsy or subtotal resection. However, recurrences occur within 1-1.5 years of initial therapy and ensue within 2 cm of the surgical margins. In recurrent GBM, repeat surgery is preferred, as it is associated with fewer complications [6,7].

Post-operative radiation therapy in GBM has resulted in clear survival advantages, establishing this as standard of care with standard radiation dose up to 60 Gy [4]. The efficacy of radiation therapy can be enhanced using radiosensitizers or modulators, usually chemotherapeutic agents [8]. Radiotherapy also functions as prime treatment modality in unresectable tumors; in recurrent GBM, repetition of radiation can be performed if the patient responded well to initial radiation.

In 2005, Stupp *et al.* [7] reported 27.2% overall survival with concurrent radiotherapy and oral temozolomide (TMZ; an alkylating cytotoxic agent) in comparison to 10.9% with radiotherapy alone. Adjuvant chemotherapy with radiotherapy has been set as standard of care for GBM to date. TMZ (Temodal®) is orally administered at a daily dose of 75 mg/m^2 throughout radiotherapy. Four weeks later, magnetic resonance imaging (MRI) is repeated, and later TMZ dose of 150 to

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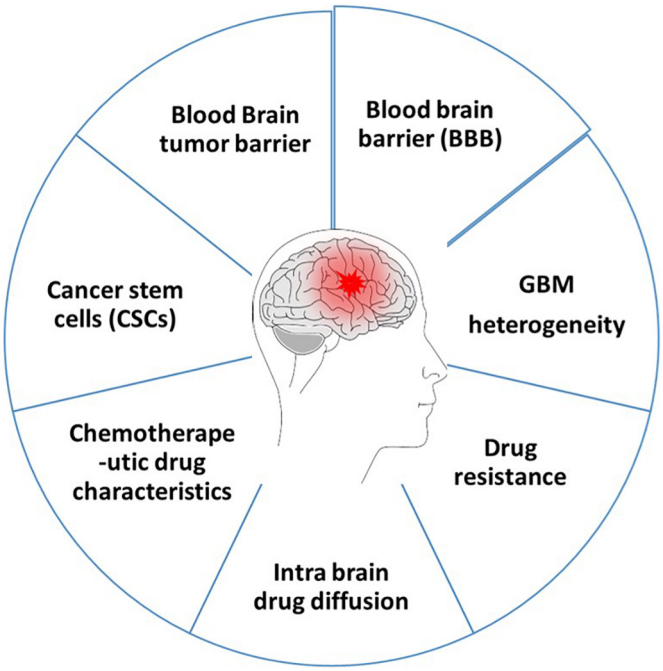

Fig. 1. Outline of GBM drug delivery challenges.

200 mg/m^2 daily for 5 consecutive days and in six cycles (28 days each cycle) is given for maintenance [4,9]. Treatment schedule extension depends on the tolerability by the patient. For treating recurrent GBM, bevacizumab (Avastin®), an antiangiogenic agent, has been used since FDA approval in 2009 (not EMA approved) following phase II trial data [15].

2. GBM drug delivery challenges

GBM is highly heterogeneous and notably challenging to drug delivery. In this section, we present the major obstacles of GBM drug delivery, and the outline of obstacles is presented in Figure 1

2.1. Blood brain barrier (BBB)

BBB, the external lining of blood vessels in the brain and spinal cord, is highly selective in permeability. The barrier properties of healthy BBB are mainly due to the presence of tight junctions between the endothelial cells, which are steadily maintained by astrocytes and pericytes. With a complex design, the BBB prevents passage of neurotoxins and microorganisms and selectively allows oxygen and nutrients into the CNS, maintaining homeostasis [10–15] [Fig. 2A]. Along with defensive functions, the BBB also prevents the entry of drugs to the CNS. Anatomical features, such as abundant presence of multidrug resistance proteins, e.g., P-glycoprotein (P-gp) and multidrug resistance proteins (MDRPs), can prevent drug accumulation inside the brain; as a result, the administered drugs remain unsuccessful or cannot achieve the wanted physiological effect [4,7,16].

In pathological conditions, the morphology and physiology of BBB are affected. GBM shows the aggressive feature of widespread infiltration into surrounding tissues. Even a single GBM cell has the capability to infiltrate and eventually develop into a tumor in series of steps that can be summarized as follows: migration of GBM cells accumulating around the existing blood vessels, removal of the astrocytic end foot processes (necessary for physiological functions of healthy BBB), and disruption of normal contact between endothelial cells and basement membranes by secreting glioma derived factors [17], such as transforming growth factor beta2 (TGF-β2), caveolin1, reactive oxygen species (ROS) and proinflammatory peptides, that induce and activate matrix metalloproteinases (MMPS) which, in turn, induce degradation of tight junctions between endothelial cells by down regulating tight junction proteins [18]. This effect leads to degradation of vessel basement membrane and surrounding extracellular matrix (ECM), migration of endothelial cells and formation of improper new blood vessels due to overexpression of VEGF, which also acts as a hypoxia-inducible factor [19] and results in neoangiogenesis. Thus, rapid endothelial proliferation of multilayer vasculature, eventually leading to loss of tight junctions, reflects the disrupted BBB [Fig. 2B].

Disrupted BBB can be clinically visualized by MRI using the T_1 contrast agent gadolinium, accumulating only within the compromised barrier regions but not in the regions with intact BBB. Furthermore, the disruption of BBB is observed only at primary tumor sites but not at infiltrative areas with migrated tumor cells, which can be several centimeters away from the visible tumor and are the main reason for the high tendency of GBM recurrence within several centimeters of the surgical resection cavity [20,21]. Additionally, BBB disruption does not necessarily imply loss of other biological mechanisms such as drug resistance. GBM patients show variable/partial and heterogeneous BBB disruption and have regions with intact BBB, which is sufficient to limit drug access to tumor cells [22,23]. GBM-associated BBB disruption leads to one of the major clinical complications of vasogenic brain edema, resulting in drastic increase of intracranial pressure due to BBB leakage [19]. The increased intracranial pressure tends to oppose the passive drug diffusion into tumor tissue.

Thus, because of variable BBB disruption, still-active drug resistance mechanisms, poor blood perfusion, and high intratumoral interstitial pressure result in therapeutic resistance of GBM [24]. Moreover, to develop effective strategies, it is crucial to understand the underlying mechanisms that affect drug accumulation.

2.2. Blood brain-tumor barrier (BBTB)

The intensity of malignancy of GBM alters the structure, function and organization of the BBB. Blood brain-tumor barrier (BBTB) is formed following the disruption of the tumor membrane and tumor deterioration. The transformation of tumor from low grade to high grade triggers the invasion of surrounding healthy brain tissue that includes damage to the BBB. Eventually, the BBB is replaced by the BBTB, limiting the penetration of drug delivery systems. Tumor expansion also needs high volumes of oxygen and nutrients that also induce expression of VEGF and angiogenesis to hypoxic areas. GBM is associated with formation of highly abnormal lymphatic vasculature and is the most vascularized among human tumors [26]. Drug permeability relies on GBM neovasculature and its heterogeneity, which shows variable vessel diameter and density and can be classified into three different types: i) continuous, nonfenestrated endothelial vasculature that exhibits similar permeability as normal vasculature, ii) continuous, fenestrated endothelial vasculature and iii) discontinuous endothelial vasculature, where drug permeability is dependent on pore area and molecular weight of the diffusing molecule [27]. The neovessels commonly show abnormal endothelial hyperplasia, pinocytic vesicles, fenestration, and opening or loss of tight junctions between endothelial cells. Although these abnormalities enhance the permeability of the BBTB, specificity of glioma and cranial microenvironment lessen the permeability [28], thereby acting as an obstacle for delivery of most antitumor agents [29,30].

2.3. Intra-brain tissue diffusion of drugs

The consequence of aggressive infiltration of GBM is migration of cancer cells into the neighboring brain tissues. Even after surgical resection, the migrated cancer cells may develop into recurrent GBM adjacent to the original tumor region. Theoretically, local drug delivery circumventing BBB should be effective against all tumor cells, but in practice, this approach is contrary for current therapies to be successful