Journal of Controlled Release 243 (2016) 29–42

Contents lists available at ScienceDirect

Journal of Controlled Release

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

Review article

# Anticancer drug-loaded hydrogels as drug delivery systems for the local treatment of glioblastoma

C. Bastiancich [a], P. Danhier [b], V. Préat [a,*,1], F. Danhier [a,*,1]

[a] Université catholique de Louvain, Louvain Drug Research Institute, Advanced Drug Delivery and Biomaterials, Avenue Mounier, B1 73.12, 1200 Brussels, Belgium
[b] Université catholique de Louvain, Louvain Drug Research Institute, Biomedical Magnetic Resonance Unit, Avenue Mounier, B1 73.08, 1200 Brussels, Belgium

ARTICLE INFO

*Article history:*
Received 20 August 2016
Received in revised form 15 September 2016
Accepted 25 September 2016
Available online 28 September 2016

*Keywords:*
Local delivery
Hydrogel
Drug delivery system
Gelation
Glioblastoma

ABSTRACT

Among central nervous system tumors, Glioblastoma (GBM) is the most common, aggressive and neurological destructive primary brain tumor in adults. Standard care therapy for GBM consists in surgical resection of the accessible tumor (without causing neurological damage) followed by chemoradiation. However, several obstacles limit the assessment of tumor response and the delivery of cytotoxic agents at the tumor site, leading to a lack of effectiveness of conventional treatments against GBM and fatal outcome. Despite the efforts of the scientific community to increase the long-term benefits of GBM therapy, at the moment GBM remains incurable. Among the strategies that have been adopted in the last two decades to find new and efficacious therapies for the treatment of GBM, the local delivery of chemotherapeutic drugs in the tumor resection cavity emerged.
In this review, our aim is to provide an overview on hydrogels loaded with anticancer drugs for the treatment of GBM recently used in preclinical and clinical studies, their advantages and major limitations for clinical translation. This review is divided in three parts: the first one describes the context of GBM and its current treatments, with a highlight on the role of local delivery in GBM treatment and the development of GBM resection murine models. Then, recent developments in the use of anticancer drug-loaded hydrogels for the treatment of GBM will be detailed. The final section will be focused on the limitations for *in vivo* studies, clinical translation and the clinical perspectives to the development of hydrogels.



**Contents**



* Corresponding authors at: Université catholique de Louvain, Louvain Drug Research Institute, Advanced Drug Delivery and Biomaterials, Avenue Mounier, 73, B1 73.12, 1200 Brussels, Belgium.
*E-mail addresses:* veronique.preat@uclouvain.be (V. Préat), fabienne.danhier@uclouvain.be (F. Danhier).
[1] These two authors equally contributed to the work.

http://dx.doi.org/10.1016/j.jconrel.2016.09.034
0168-3659/

## 1. Introduction

### 1.1. Glioblastoma

Brain tumors only count 2% of the adult population affected by cancer. However, they are considered among the worst diseases as they have a direct impact on patient's life from a physical, psychological and neurological point of view [1]. Among brain tumors, Glioblastoma (GBM) is the most common and aggressive in adults, and also the most feared by patients, physicians and oncologists [2,3]. Indeed, GBM has been classified as grade IV astrocytoma as it is highly malignant and arises from astrocytes or supportive brain tissue [4]. Preventive measures, such as life style changes, early diagnosis and treatment unfortunately do not impede the development of the disease and do not improve its outcome, precluding the utility of screening for this tumor [1]. Based on the clinical history of the tumor, GBM can be divided into primary GBM (90%) or secondary GBM (10%): in the first case the tumor arises in an acute *de novo* manner without previous lower grade pathology or symptoms, while the secondary GBM derives from the progressive evolution and transformation of lower grade astrocytomas and normally affects younger patients. The two subtypes of GBM present different genetic profiles and can be identified by specific cell markers but are morphologically and clinically indistinguishable. Moreover, both have the same poor prognosis (median survival below 15 months) and remain incurable [5]. Signs and symptoms from GBM usually result from infiltration or compression of normal brain by tumor, edema, hemorrhage or increased intracranial pressure and include headaches, seizures, focal neurologic deficits and changes in mental status [6]. Despite the low number of patients affected by this disease (the US and EU incidence is 3 in 10,000 persons) [7], in the last decades many researchers have focused their attention to find new efficacious treatment strategies to improve the quality of life of patients affected by GBM and their clinical outcome.

Several obstacles limit the assessment of tumor response and the delivery of cytotoxic agents leading to a lack of effectiveness of GBM treatments (Fig. 1): (i) the anatomical location of the tumor in the brain often impedes a complete surgical resection without damaging the neurological tissue and affects the cognitive functions of the patient. Moreover, the central nervous system (CNS) barriers (blood cerebrospinal fluid barrier; arachnoid barrier; blood-brain barrier, BBB; blood-tumor barrier) represent a challenge to the delivery of cytotoxic drugs at therapeutic concentrations at the tumor site. (ii) GBM is highly heterogeneous at all levels, from the tissue level to the molecular and genetic point of view to the cell type [2,8]. This heterogeneity, represented also within the same tumor, leads to high variability in tumor histopathology making the classification of these tumors very difficult and resulting in low predictability of tumor response to treatments [9]; (iii) the hallmark characteristics of GBM are uncontrolled cellular proliferation, propensity for necrosis and angiogenesis, resistance to apoptosis, high genomic instability, chemoresistance and fatal outcome [5]. GBM cells are able to extend their tendrils into the normal surrounding parenchyma infiltrating diffusely beyond the primary lesion in the early stages of tumor development (GBM is also known as “octopus tumor”) [10]. Many individual genes implicated in GBM cells migration and invasion have been identified and their presence has been correlated with poor patient survival [11]. It has also been shown that GBM invasion is

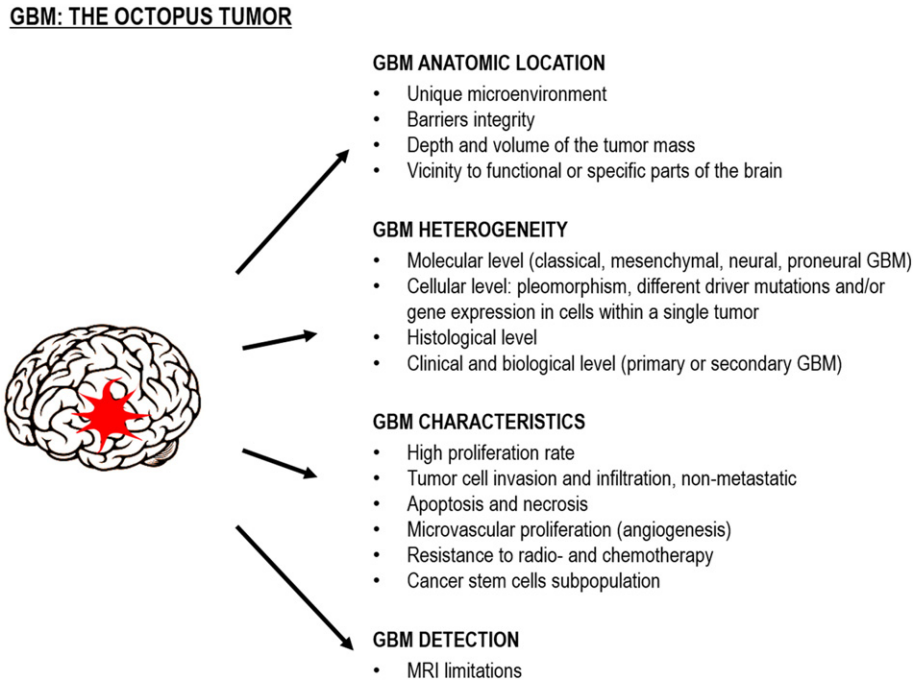


**Fig. 1.** Obstacles for effective treatment of GBM that contribute to its fatal outcome.