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Review

Breaching barriers in glioblastoma. Part I: Molecular pathways and novel treatment approaches

Ana Miranda[a,b], María Blanco-Prieto[c], João Sousa[a,b], Alberto Pais[d], Carla Vitorino[a,b,*]

[a] Faculty of Pharmacy, University of Coimbra, Portugal
[b] Pharmacometrics Group of the Centre for Neurosciences and Cell Biology (CNC), University of Coimbra, Portugal
[c] Department of Pharmacy and Pharmaceutical Technology, School of Pharmacy, University of Navarra, Spain
[d] Coimbra Chemistry Center, Department of Chemistry, University of Coimbra, Portugal

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ABSTRACT

Glioblastoma multiforme (GBM) is the most common primary brain tumour, and the most aggressive in nature. The prognosis for patients with GBM remains poor, with a median survival time of only 1–2 years. The treatment failure relies on the development of resistance by tumour cells and the difficulty of ensuring that drugs effectively cross the dual blood brain barrier/blood brain tumour barrier.

The advanced molecular and genetic knowledge has allowed to identify the mechanisms responsible for temozolomide resistance, which represents the standard of care in GBM, along with surgical resection and radiotherapy. Such resistance has motivated the researchers to investigate new avenues for GBM treatment intended to improve patient survival.

In this review, we provide an overview of major obstacles to effective treatment of GBM, encompassing biological barriers, cancer stem cells, DNA repair mechanisms, deregulated signalling pathways and autophagy. New insights and potential therapy approaches for GBM are also discussed, emphasizing localized chemotherapy delivered directly to the brain, immunotherapy, gene therapy and nanoparticle-mediated brain drug delivery.

Contents

* Corresponding author at: Faculty of Pharmacy, University of Coimbra, Portugal.
E-mail address: csvitorino@ff.uc.pt (C. Vitorino).

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1. Glioblastoma multiforme

1.1. Clinical and epidemiological aspects

About 5–6 cases out of 100,000 people are diagnosed with primary malignant brain tumours per year, and 80% of them are malignant gliomas. (MGs) (Alifieris and Trafalis, 2015; Schwartzbaum et al., 2006; Stupp et al., 2010). Thus, the most common group of primary brain tumours are MGs, which include astrocytomas, oligodendrogliomas and ependymomas. The World Health Organization (WHO) subcategorized MGs into grade III/IV tumours (such as anaplastic oligoastrocytoma, anaplastic astrocytoma, anaplastic ependymomas and anaplastic oligodendroglioma), as well as grade IV/IV tumours, in the case of glioblastoma multiforme (GBM) (Alifieris and Trafalis, 2015; Louis et al., 2007).

GBM is considered the most common malignant form of primary brain cancer in adults, once it represents more than half of MG cases (Ohgaki and Kleihues, 2005). GBM is also considered the most aggressive and lethal form of brain tumour due to high degree of tumour cell infiltration into surrounding brain tissue (Séhédic et al., 2015). Moreover, some of lower WHO grade MGs can recur, progress, or transform into GBMs, being termed secondary GBMs (over 10% of diagnosed GBM cases). The remaining 90% of diagnosed GBM cases are primary GBMs, also known as *de novo* GBM tumours (Kim et al., 2015; Urbańska et al., 2014). Primary and secondary GBMs have a similar morphology, despite the different molecular pathways underlying their developments (Urbańska et al., 2014; Karcher et al., 2006). Nevertheless, GBMs may take on a variety of appearances, depending on the level of necrosis exhibited and the possible existence of haemorrhage. GBM usually occur within the white matter in the form of heterogeneous lesion, but tend to spread rapidly into the surrounding brain tissue (Ellor et al., 2014).

The mean age of primary and secondary GBM patients is 62 and 45, respectively, although there is a greater variation in age distribution with the secondary type. It is then realized that GBM rarely appears during childhood and adolescence, representing only 8.8% of all central nervous system (CNS) cancers seen in these age groups (Adamson et al., 2009). GBMs that appear in children and adults do not usually show morphological differences. In fact, the only significant variant among them concerns the proliferative activity of the glioma cells, which is higher in the case of children (Urbańska et al., 2014). On the other hand, while primary GBM occurs more frequently in males (M:F ratio = 3:1), the opposite happens with secondary GBM (Adamson et al., 2009; Ohgaki et al., 2004).

The exact etiology of GBM has not been clarified up to now. GBM is expected to be a spontaneous tumour, although there is still 1% of all GBM cases associated with familial form. The potential risk factors for glioma are not well understood (Schwartzbaum et al., 2006; Urbańska et al., 2014; Adamson et al., 2009). Exposure to ionizing radiation, electromagnetic fields and certain metals, as well as some pesticides, polycyclic aromatic compounds and solvents, is predicted to increase the likelihood of developing GBM (Urbańska et al., 2014; Adamson et al., 2009).

Gold-standard treatment of GBM include tumour resection, radiotherapy and chemotherapy. Unfortunately, the tumour tends to spread rapidly and to return after treatment, resulting in a very poor outcome associated with a bad prognosis. GBM is an incurable malignancy, wherein the median survival of patients with this tumour is about 18 months. Only about 30% of patients achieve 2-year survival and fewer than 10% survive more than 3 years. Exceptionally, a small number of patients can survive for a longer period (Kim et al., 2015; Auffinger et al., 2015; Stupp et al., 2005; Aldape et al., 2015; Lu et al., 2016). According to a population based study, the risk of death is higher during the first quarter of the second year of GBM post-diagnosis, whereas the mortality decreases to half of its rate at 2.5 years. These results suggest that survival rate is lower in newly diagnosed patients compared to those diagnosed for more than 2 years (Thakkar et al., 2014; Smoll et al., 2013).

GBM is known by cellular heterogeneity and drug-resistance nature of its cells, leading to high rates of recurrence and a short median survival. All of these factors make GBM one of the most lethal cancers (Kim et al., 2015; Pourgholi et al., 2016).

1.2. Standard treatment

Advances in oncology research and treatments have been remarkable, but GBM remains one of the greatest challenges in the management of cancer patients worldwide (Adamson et al., 2009). Ideally, GBM treatment should induce tumour regression and simultaneously improve the median survival time of the patients (Urbańska et al., 2014).

The standard therapy for GBM has been the same for many decades and involves maximum feasible surgical resection, followed by radiation plus concomitant chemotherapy with temozolomide (TMZ), followed by adjuvant TMZ (Ellor et al., 2014; Patel et al., 2014a). However, carboplatin, procarbazine and the nitrosourea compounds carmustine (BCNU) and lomustine (CCNU) have also been considered. In the past, both cisplatin and carboplatin were used as first line agents in GBM treatment; but cisplatin-induced ototoxicity and nephrotoxicity, as well as the myelosuppression caused by carboplatin, have limited desirability and risk/benefit ratio value of these agents. Furthermore, the combination use of CCNU, procarbazine and vincristine (PCV) for GBM has been greatly discouraged, mainly due to inferior results when compared with TMZ and toxicity issues as well (Ellor et al., 2014; Fine et al., 1993; Murray et al., 2011).

According to comparative studies involving several chemotherapeutic agents, TMZ was the drug that provided the highest median survival time in patients (Urbańska et al., 2014). Moreover, in a large, randomized phase III trial, radiotherapy alone was compared with radiotherapy along with TMZ treatment. Combination therapy resulted in an improved median overall survival from 12.1 to 14.6 months and an increase in the 2-year survival rate from 10% to 27%. The addition of TMZ to radiotherapy is associated