

ABSTRACT

Int Rev Immunol. 2022 Aug 8;1-24. doi: 10.1080/08830185.2022.2101647. Online ahead of print.

Combinatorial approaches to effective therapy in glioblastoma (GBM): Current status and what the future holds.

Asija S(1), Chatterjee A(2)(3), Yadav S(2)(3), Chekuri G(2)(3), Karulkar A(1), Jaiswal AK(1), Goda JS(2)(3), Purwar R(1).

Author information:

(1)Department of Biosciences & Bioengineering, Indian Institute of Technology, Mumbai, India.

(2)Department of Radiation Oncology, Tata Memorial Center, Mumbai, Maharashtra, India.

(3)Homi Bhabha National Institute, Mumbai, Maharashtra, India.

The aggressive and recurrent nature of glioblastoma is multifactorial and has been attributed to its biological heterogeneity, dysfunctional metabolic signaling pathways, rigid blood-brain barrier, inherent resistance to standard therapy due to the stemness property of the gliomas cells, immunosuppressive tumor microenvironment, hypoxia and neoangiogenesis which are very well orchestrated and create the tumor's own highly pro-tumorigenic milieu. Once the relay of events starts amongst these components, eventually it becomes difficult to control the cascade using only the balanced contemporary care of treatment consisting of maximal resection, radiotherapy and chemotherapy with temozolamide. Over the past few decades, implementation of contemporary treatment modalities has shown benefit to some extent, but no significant overall survival benefit is achieved. Therefore, there is an unmet need for advanced multifaceted combinatorial strategies. Recent advances in molecular biology, development of innovative therapeutics and novel delivery platforms over the years has resulted in a paradigm shift in gliomas therapeutics. Decades of research has led to emergence of several treatment molecules, including immunotherapies such as immune checkpoint blockade, oncolytic virotherapy, adoptive cell therapy, nanoparticles, CED and BNCT, each with the unique proficiency to overcome the mentioned challenges, present research. Recent years are seeing innovative combinatorial strategies to overcome the multifactorial resistance put forth by the GBM cell and its TME. This review discusses the contemporary and the investigational combinatorial strategies being employed to treat GBM and summarizes the evidence accumulated till date.

Plain Language Summary: Glioblastoma is a form of brain tumor which typically leads to death in almost all patients. Over the last two decades, traditional treatment strategies such as surgery, radiotherapy and chemotherapy have been combined as standard therapy. Together, these aggressive treatment strategies have provided modest survival benefit with acceptable toxicity. However, relapse is the invariable norm resulting in death in the overwhelming majority of patients. Relapse occurs due to multiple factors such as inability of drugs to cross blood-brain barrier, immunosuppressive tumor microenvironment, stemness nature of glioma cells, tumor heterogeneity and enhanced hypoxia and angiogenic factors. Therefore, there is an urgent need to develop an innovative treatment approach to treat glioblastoma. Recently, several treatment strategies known as immunotherapies including CAR T cell therapy, dendritic cell vaccines, immune checkpoints blockade and oncolytic virus, nano particles and gene editing/silencing technology have demonstrated promising results in preclinical and few clinical trials. Furthermore, to increase the efficacy of these novel strategies, combinatorial approaches are being implemented for the treatment. This includes CAR T cell therapy in combination with small molecules, immune checkpoint inhibitors and oncolytic virus and nanoparticles plus gene editing, silencing or immune checkpoints inhibitors. These treatments have shown exciting results in preclinical settings and few of these trials are in progress. The

review summarizes these combinatorial novel approaches and discusses them in detail.

DOI: 10.1080/08830185.2022.2101647

PMID: 35938932