RECIMA21 - REVISTA CIENTÍFICA MULTIDISCIPLINAR
ISSN 2675-6218

GLIOBLASTOMA MULTIFORME: A BRIEF LITERATURE REVIEW

GLIOBLASTOMA MULTIFORME: UMA BREVE REVISÃO DA LITERATURA

GLIOBLASTOMA MULTIFORME: UNA BREVE REVISIÓN DE LA LITERATURA

Yasmim Fernandes Moniz[1]

e453118
https://doi.org/10.47820/recima21.v4i5.3118

RECEIVED: 03/14/2023 APPROVED: 04/14/2023 PUBLISHED: 04/29/2023

ABSTRACT
The objective of this article is to review the current state of knowledge about glioblastoma multiforme. Gliomas originated in astrocytes can be classified into four types: Pilocytic Astrocytoma, Fibrillary Astrocytoma, Anaplastic Astrocytoma and Glioblastoma Multiforme. Glioblastoma Multiforme is the most malignant and aggressive type of these. The risk factors for this tumor are still poorly understood, but it has been proven that ionizing radiation can be one of them. The diagnosis is made through the analysis of the critical manifestations and with complementary examinations such as computed tomography and magnetic resonance imaging. The treatments used against this type of tumor are maximum tumor resection, radiotherapy, chemotherapy, Tumor-Treating Fields, Bevacizumab, Oncolytic Viruses. Although there are several types of treatment, the prognosis of this tumor remains limited. More studies are needed to investigate the effectiveness of the treatments used, as well as the access of the general public to these treatments in the public health system.

KEYWORDS: Classification. Diagnosis. Etiology. Glioblastoma. Treatment.

RESUMO
O objetivo deste artigo é revisar o atual estado de conhecimento acerca do glioblastoma multiforme. Os gliomas originados nos astrócitos podem ser classificados em quatro tipos: Astrocitoma Pilocítico, Astrocitoma Fibrilar, Astrocitoma Anaplásico e Glioblastoma Multiforme. O Glioblastoma Multiforme é o tipo mais maligno e agressivo destes. Os fatores de risco deste tumor ainda são pouco conhecidos, porém foi comprovado que a radiação ionizante pode ser um deles. O diagnóstico é realizado através da análise das manifestações críticas e com exames complementares como a tomografia computadorizada e a ressonância magnética. Os tratamentos usados contra esse tipo de tumor são a ressecção máxima do tumor, radioterapia, quimioterapia, Tumor-Treating Fields, Bevacizumab, Vírus Oncolíticos. Embora existam vários tipos de tratamento, o prognóstico deste tumor continua limitado. São necessários mais estudos que investiguem a efetividade dos tratamentos utilizados, bem como o acesso do público em geral a esses tratamentos no sistema público de saúde.

PALAVRAS-CHAVE: Classificação. Diagnóstico. Etiologia. Glioblastoma. Tratamento.

RESUMEN
El objetivo de este artículo es revisar el estado actual del conocimiento sobre el glioblastoma multiforme. Los gliomas originados en astrocitos se pueden clasificar en cuatro tipos: astrocitoma pilocítico, astrocitoma fibrilar, astrocitoma anaplásico y glioblastoma multiforme. El glioblastoma multiforme es el tipo más maligno y agresivo de estos. Los factores de riesgo de este tumor aún no se conocen bien, pero se ha demostrado que la radiación ionizante puede ser uno de ellos. El diagnóstico se realiza mediante el análisis de las manifestaciones críticas y con exámenes complementarios como la tomografía computarizada y la resonancia magnética. Los tratamientos utilizados contra este tipo de tumor son la resección tumoral máxima, radioterapia, quimioterapia, Campos Tumorales, Bevacizumab, Virus Oncolíticos. Aunque existen varios tipos de tratamiento, el pronóstico de este tumor sigue siendo limitado. Se necesitan más estudios para investigar la

[1] Universidade de Mogi das Cruzes (UMC).

RECIMA21 - REVISTA CIENTÍFICA MULTIDISCIPLINAR
ISSN 2675-6218

efectividad de los tratamientos utilizados, así como el acceso del público en general a estos tratamientos en el sistema de salud pública.

PALABRAS CLAVE: Clasificación. Diagnóstico. Etiología. Glioblastoma. Tratamiento.

INTRODUCTION

Nervous system cancer represents approximately 2% of all malignant neoplasms worldwide. Its estimated risk is higher in men, with an annual risk of 5 new cases per 100,000 men and 4 per 100,000 women (RODRÍGUEZ-CAMACHO, 2022).

Glial tumors (tumors originating from glia cells) represent the majority of primary brain tumors, regardless of age group (GOVINDAN et al., 2011). This tumor type can originate in any glia cell type and 50-60% of gliomas are glioblastomas (GBM), the most malignant variation.

Little is known about the risk factors for glioblastoma, but therapeutic irradiation is known to be one of these factors. Some work suggests that perhaps radiation generated by radiofrequency and mobile telephony could be correlated with the occurrence of this tumor, but findings are still scarce (RODRÍGUEZ-CAMACHO, 2022).

This type of tumor is a challenge for the medical community due to its ability to infiltrate adjacent tissues and be typically located in the supratentorial areas: frontal, parietal, temporal and occipital lobe (FRANCIPANE et al., 2021).

The histological characteristic of glioblastoma multiforme is prominent nuclear and cellular atypia, occurrence of mitotic figures, extensive areas of cellular necrosis and atypical vascular proliferation (GRITSCH; BATCHELOR; GONZALEZ, 2022).

Even with the implementation of new strategies and the advancement of therapies against GBM, the condition remains with a limited prognosis and affected individuals have little prospect of lasting survival (JANJUA et al., 2021).

In view, the current scenario, it is necessary to understand the pathophysiological mechanisms and the effectiveness of treatments for a better coping of this pathology. Thus, the aim of this study is to review the current state of knowledge about glioblastoma multiforme.

METHODOLOGY

A literature review was conducted. The search for data in specific books in the oncology area, as well as in electronic databases of scientific articles, was carried out. The articles were searched in PubMed, Scielo, Google Scholar, and Cochrane Library. The keywords used were: glioblastoma (always associated with the Boolean "AND"), diagnosis, treatment, etiology, characteristics. The material was included in the data synthesis if it met at least one of the established topics of knowledge about Glioblastoma Multiforme: diagnosis, treatment, tumor characteristics and etiology. Priority in the data synthesis was given to the most recently published articles/books.

RECIMA21 - REVISTA CIENTÍFICA MULTIDISCIPLINAR
ISSN 2675-6218

RESULTS AND DISCUSSION

ASTRONYCITS: CHARACTERISTICS

There are two types of astrocytes: fibrous and protoplasmic. The fibrous ones are found primarily in the white substance. The protoplasmic cells are found primarily in the gray matter. Protoplasmic cells are also differentiated by having shorter, thicker and more branched extensions than fibrous astrocytes (SPLITTGERBER, 2021; PARPURA et al., 2012).

Astrocytes have numerous functions, such as support for nerve cells, formation of framework in the embryonic process for the migration of immature neurons, electrical insulator (which prevents an excitation during of surrounding neurons the communication between adjacent neurons), perform phagocytosis and glycogen storage (SPLITTGERBER, 2021; PARPURA et al., 2012) In addition, it is suggested that astrocytes secrete cytokines, which generate immune responses in the face of diseases in the nervous system.

ORIGIN CELLS

The origin of Glioblastoma Multiforme can hardly be identified, however studies suggest that it may originate from neural stem cells or glial precursors, these have infiltrative capacity and cause endothelial death, necrosis and a typically inflammatory pattern (RODRÍGUEZ-CAMACHO et al., 2022).

There is group of neural progenitor cells with the ability to enter mitosis and promote neural plasticity related to learning and memory (WIRSCHING; GALANIS; WELLER, 2016).

A subpopulation of glioblastoma cells called glioma stem cells share numerous of these characteristics of neural progenitor cells, including localization, self-renewal, and multi-lineage differentiation (WIRSCHING; GALANIS; WELLER, 2016). Although preclinical data indicate that resistance to treatments could be associated with the peculiarities of this cell type, no specific protocol/treatment has been developed for these cells.

ETIOLOGY

Studies suggest some risk factors such as exposure to chemical substances (formaldehyde, vinyl chloride and organic solvents), nitrous preservatives, pesticides, petroleum derivatives, tobacco and drugs. However the only one proven so far is ionizing radiation (radiography and radiotherapy) (VILELA; HACKBART, 2008).

There is a higher risk of glioma development in some genetic diseases, such as neurofibromatosis 1 and 2, tuberous sclerosis, Li-Fraumeni syndrome, retinoblastoma and Turcot syndrome, but less than 1 % of patients with glioblastoma have these conditions (DAVIS, 2016).

RECIMA21 - REVISTA CIENTÍFICA MULTIDISCIPLINAR
ISSN 2675-6218

CLASSIFICATION OF THE TYPES OF ASTROCYTOMAS

Gliomas are brain tumors that originate from glia cells, the denomination of each type of tumor varies according to the cell that gave rise to it. Thus, astrocytomas are tumors originating from astrocytes (VILELA; HACKBART, 2008).

According to the classification of the Health Organization (WHO), astrocytomas are divided into 4 groups:

- Pilocytic Astrocytoma
- Fibrillary Astrocytoma
- Anaplastic Astrocytoma
- Glioblastoma Multiforme

According to pathological and histological criteria, the astrocytomas can be differentiated as follows: changes in capillarity define the presence of a neoplasm that can be indicative of a Pilocytic Astrocytoma. When there is cell atypia it is indicative of a Fibrillary Astrocytoma, and when there is an association with mitotic activity there is an Anaplastic Astrocytoma. The presence of endothelial hyperplasia and/or necrosis indicates Glioblastoma Multiforme (VILELA; HACKBART, 2008).

Glioblastomas can also be defined considering the origin of their appearance. If there is no previous factor associated with it, it is classified as primary and if it originates from another type of tumor that was not the glioblastoma, it is classified as secondary (DAVIS, 2016).

CLINICAL MANIFESTATIONS

The symptoms and clinical manifestations of glioblastoma depend on the extent of the lesion, its location, and the structures that have been compromised (DAVIS, 2016).

Patients often present with symptoms related to increased intracranial pressure (headache and neurological deficits). The most common clinical manifestations being headache, epilepsy, seizures, vomiting, personality disorders, endocrine syndromes (DAVIS, 2016).

DIAGNOSIS

The diagnosis is made in conjunction with the physical examination and complementary imaging examinations such as magnetic resonance imaging and computed tomography. When the investigation of the clinical history is performed, the clinician should consider that the signs and symptoms will depend on the location of the tumor and therefore, all clinical manifestations should be analyzed (HEEMANN G; HEEMANN A, 2018; VILELA; HACKBART, 2008).

In the physical examination, it is necessary to be alert for signs of increased intracranial pressure, such as headache, nausea, vomiting, cognitive deficit, papilledema, ataxia, cranial nerve palsy, hemiparesis, and altered reflexes (HEEMANN G; HEEMANN A, 2018; VILELA; HACKBART, 2008).

RECIMA21 - REVISTA CIENTÍFICA MULTIDISCIPLINAR
ISSN 2675-6218

In complementary imaging exams, the Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) stand out. These exams reveal the expansive nature of the brain tumor. The CT exam verifies the volume of the neoplastic tissue and the adjacent edema. The MRI, on the other hand, verifies the rupture of the blood-brain barrier inside the tumor, which denotes the extravasation of the contrast agent. However, low-level gliomas generally do not absorb the contrast agent (VILELA; HACKBART, 2008).

TRADITIONAL TREATMENTS

One of the most well accepted protocols currently for treatment is the Stupp Protocol which consists of maximum safe surgical section followed by radiotherapy for 6 weeks and concomitant daily doses of thermozolomide (chemotherapy), followed by 6 adjuvant maintenance cycles of thermozolomide administered for 5 days every 28 days (RODRÍGUEZ-CAMACHO et al., 2022).

The goal of surgery is to achieve total resection of the tumor, as safely as possible, and ensuring the patient's functional status. During this surgery it is possible to reduce the tumor volume, perform histological diagnosis, and investigate tumor genotyping. When compared to partial and total resection, the latter promotes a greater chance of survival (RODRÍGUEZ-CAMACHO et al., 2022).

Radiation therapy is prescribed with the goal of achieving local control of the tumor without causing neurotoxicity. This therapy is usually delivered over a 6-week period of 2 Gy and total dose fractions of 40-60 Gy (RODRÍGUEZ-CAMACHO et al., 2022; WU et al., 2021).

Chemotherapy is performed orally with the drug thermozolomide, an ankylating agent that directly targets damage to tumors by methylation of DNA purine bases (WU et al., 2021). The drug has the ability to penetrate the blood-brain barrier and is the current first-choice systemic therapy for the treatment of Glioblastoma Multiforme (RODRÍGUEZ-CAMACHO et al., 2022). Its application concomitantly with radiotherapy is associated with a more attenuated disease progression, higher survival rate and in addition, thermozolomide is associated with the ability to sensitize to radiation (making exposed cells more susceptible to cell death) (HART et al., 2013).

OTHER TYPES OF TREATMENT

Other types of strategies for the treatment of glioblastoma multiforme are emerging in the literature. Although many of these need further studies to prove and quantify their effect, but they present important perspectives for the future treatment of glioblastoma multiforme.

Tumor-Treating Fields (TTF'S)

This type of procedure is a physical treatment that uses air transducers applied directly to the scalp to promote alternating electric fields to treat newly diagnosed or recurrent Glioblastoma Multiforme. TTF'S generate selective toxicity in rapidly dividing cells, causing neural depolarization and impairing microtubule formation during mitosis (FRANCIPANE et al., 2021; RODRÍGUEZ-CAMACHO et al., 2022).

RECIMA21 - REVISTA CIENTÍFICA MULTIDISCIPLINAR
ISSN 2675-6218

Bevacizumab

Glioblastomas have the characteristic of being highly vascularized, this stems from the overexpression of endothelial growth factor. Bevacuzumab is a monoclonal antibody that acts against this endothelial growth factor. However, more studies are needed to verify the effectiveness of this treatment (RODRÍGUEZ-CAMACHO et al., 2022). It is currently used primarily for the treatment of recurrent glioblastomas (WU et al., 2021).

Oncolytic Viruses

This category consists of the manipulation of genetically encoded viruses for the purpose of fighting cancer cells. These viruses are usually applied to the tumor region or are administered systemically. Some studies involving this type of proposal have obtained positive results in relation to prolonging the life of patients (4 to 14 years) (FRANCIPANE et al., 2021).

CONSIDERATIONS

Glioblastoma multiforme is a brain cancer, originating in the cells of the astrocytes, and among the types of gliomas it is the most aggressive. The factors associated with its occurrence are still uncertain, but exposure to radiation is a determining factor in the development of this tumor.

The best accepted treatment is the Stupp Protocol, which consists in the maximum resection of the tumor area, and the application of radiotherapy and oral chemotherapy (thermozolomide) concomitantly. However, there are other treatments that have been researched and applied to control this tumor (Tumor-Treating Fields (TTF'S), Bevacizumab, Oncolytic Viruses).

Although medicine has advanced in the understanding of this tumor, the prognosis of life remains limited due to the occurrence of tumor recurrences and its highly infiltrative and resistant character. Thus, more studies are needed on the characteristics of this tumor, as well as treatment strategies. In addition, it becomes necessary to verify the access to these treatments offered by the public health system.

REFERENCES

DAVIS, Mary Elizabeth. Glioblastoma: Overview of Disease and Treatment. **Clin J Oncol Nurs**., v. 20, n. 5, 2016.

FRANCIPANE, Maria Giovanna; DOURADINHA, Bruno; CHINNICI, Cinzia Maria; RUSSELLI, Giovanna; CONALDI, Pier Giulio; IANNOLO, Gioacchin. Zika virus: A new therapeutic candidate for glioblastoma treatment. **International Journal of Molecular Sciences**, [S. l.], v. 22, n. 20, 2021. DOI: 10.3390/ijms222010996.

GOVINDAN, Aparna; CHAKRABORTI, Shrijeet; MAHADEVAN, Anita; CHICKABASAVAIAH, Yasha T.; SANTOSH, Vani; SHANKAR, S. K. Histopathologic and immunohistochemical profile of spinal glioblastoma: a study of six cases. **Brain tumor pathology**, Japan, v. 28, n. 4, p. 297–303, 2011. DOI: 10.1007/s10014-011-0041-5.

RECIMA21 - REVISTA CIENTÍFICA MULTIDISCIPLINAR
ISSN 2675-6218

GRITSCH, Simon; BATCHELOR, Tracy T.; GONZALEZ, Castro L. Nicolas. Diagnostic, therapeutic, and prognostic implications of the 2021 World Health Organization classification of tumors of the central nervous system. **Cancer**, United States, v. 128, n. 1, p. 47–58, 2022. DOI: 10.1002/cncr.33918.

HART, Michael G.; GARSIDE, Ruth; ROGERS, Gabriel; STEIN, Ken; GRANT, Robin. Temozolomide for high grade glioma. **Cochrane Database of Systematic Reviews**, [S. l.], v. 2013, n. 4, 2013. DOI: 10.1002/14651858.CD007415.pub2.

HEEMANN, Gabriel Carvalho; HEEMANN, Antônio Carlos Cunha. Glioblastoma multiforme recém-diagnosticado: diagnóstico e tratamento cirúrgico inicial. **Acta méd**., (Porto Alegre), p. 163–172, 2018.

JANJUA, Taskeen Iqbal et al. Frontiers in the treatment of glioblastoma: Past, present and emerging. **Advanced Drug Delivery Reviews**, [S. l.], v. 171, p. 108–138, 2021. DOI: https://doi.org/10.1016/j.addr.2021.01.012. Disponível em: https://www.sciencedirect.com/science/article/pii/S0169409X21000223.

PARPURA, Vladimir et al. Glial cells in (patho)physiology. **Journal of Neurochemistry**, [S. l.], v. 121, n. 1, p. 4–27, 2012. DOI: 10.1111/j.1471-4159.2012.07664.x.

RODRÍGUEZ-CAMACHO, Alejandro et al. Glioblastoma Treatment: State-of-the-Art and Future Perspectives. **International Journal of Molecular Sciences**, [S. l.], v. 23, n. 13, p. 1–35, 2022. DOI: 10.3390/ijms23137207.

SPLITTGERBER, Ryan. **Snell Neuroanatomia Clínica**. Porto Alegre: Grupo GEN, 2021. *E-book*. ISBN 9788527737913.

VILELA, Manuel Augusto Pereira; HACKBART, Aline de Araújo. **Oncologia básica**: experiência multidisciplinar da UFPel. Pelotas: Editora Universitária UFPel, 2008. 404 p.

WIRSCHING, Hans Georg; GALANIS, Evanthia; WELLER, Michael. Glioblastoma. **Handbook of Clinical Neurology**, [S. l.], v. 134, p. 381–397, 2016. DOI: 10.1016/B978-0-12-802997-8.00023-2.

WU, Wei; KLOCKOW, Jessica L.; ZHANG, Michael; LAFORTUNE, Famyrah; CHANG, Edwin; JIN, Linchun; WU, Yang; DALDRUP-LINK, Heike E. Glioblastoma multiforme (GBM): An overview of current therapies and mechanisms of resistance. **Pharmacological Research**, [S. l.], v. 171, n. May, p. 105780, 2021. DOI: 10.1016/j.phrs.2021.105780. Disponível em: https://doi.org/10.1016/j.phrs.2021.105780.