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Advances in the Treatment of Malignant Gliomas: A Review of the Literature

Andrés Fonnegra Caballero[1],Thiago Andrés Navarro Álvarez[2],Jaime Antonio Navarro Álvarez[3] , María Sofía González Casagua[4], Ricardo Andrés Novoa Álvarez[5]

1. *https://orcid.org/0000-0003-0453-5646 Medical School, Navarra University Foundation, Neiva, Huila, Colombia*
2. *https://orcid.org/0000-0002-3272-471Medical School, Navarra University Foundation, Neiva, Huila, Colombia*
3. *Corresponding Author's Email: thiago.navarro@uninavarra.edu.co - https://orcid.org/0009-0006-0464-7380 Medical School, Navarra University Foundation, Neiva, Huila, Colombia*
4. *https://orcid.org/0000-0002-4023-3517 Medical School, Navarra University Foundation, Neiva, Huila, Colombia*
5. *https://orcid.org/0000-0001-9892-3468 Medical School, Navarra University Foundation, Neiva, Huila, Colombia*

Abstract

Goal: The objective of this review is to describe the latest therapeutic advances used for managing patients diagnosed with recurrent malignant gliomas.

Methods: A comprehensive bibliographic review was conducted in the PubMed, Scopus, EBSCO, and Elsevier databases; articles published between 2018 and 2023 were selected and analyzed.

Results: The management protocol for patients with glioblastomas depends on the imaging diagnosis of the lesion and time of diagnosis; thus, significant differences can be found in the therapeutic strategies between the de novo diagnoses and recurrences. Thus, de novo glioblastomas have standardized protocols substantiated by maximum safe resection, followed by cycles of chemotherapy and radiation therapy. Adjuvant therapies are used for recurrent glioblastomas, and among them, molecular therapies and immunotherapy stand out. However, despite the advent of genetic modification and neurosurgery technologies, there has been no significant impact on the medium- and long-term survival of patients with glioblastomas.

Conclusions: Therapeutic measures are based on neurosurgery to achieve maximal safe surgical resections associated with postoperative chemotherapy and radiotherapy sessions with lower secondary complications. In patients with recurrent neoplasms, the use of adjuvant therapies such as bevacizumab and immunotherapies is indicated, though limited therapeutic results and minimal impacts have been found for the overall survival rates. Hence, extensive clinical follow-up is required to improve the understanding of the disease and effectiveness of these novel therapeutic alternatives.

Keywords: Glioblastoma, Radiotherapy, Chemotherapy, Immunomodulation, Neurosurgery.

Introduction

Gliomas are the most common form of primary tumors of the central nervous system (CNS) [1]. They are mainly characterized by their high invasive potential and their rapid progression, generating high overall 18-month mortality rates, high recurrence rates, high health care costs, and poor therapeutic results, even with adequate medical management; this is true especially in advanced stages such as glioblastoma multiforme (GBM), which makes gliomas a fatal disease [1–5]. Currently, the comprehensive treatment of patients with gliomas is made

up of aggressive multimodal regimes that are mainly based on maximum safe surgical resection and concomitant chemoradiation therapy, which depend largely on the patient's age, the genotyping of the tumor, and its degree of malignancy [4–6].

Currently, surgical interventions are faced with those challenges related to inaccurate demarcation of the tumor margin. This is because during neurointerventions sometimes generates partial neoplastic resections that are potentially associated with secondary neurological compromise and an increased risk of the tumor cell spreading to the adjacent areas of the brain[7,8]. When this occurs, real-time intraoperative neuroimages must be used to improve the evaluation of the resection area, preserve neuronal tissue, minimize the times of intervention, and facilitate the use of minimally invasive surgical techniques associated with novel therapeutic alternatives to improve the quality of life of patients and reduce the operational risks [8].

Thus, technical-scientific advances give rise to innovative neurosurgical treatments that are supported by computational and neuro navigation technologies that facilitate access to sites of surgical interest through safer and more effective procedures, among which include robotic-assisted surgery, radiation therapy, and adjuvant therapies [9,10]. Working in this context, the objective of the present review is to describe the latest therapeutic advances used to manage patients diagnosed with recurrent malignant gliomas.

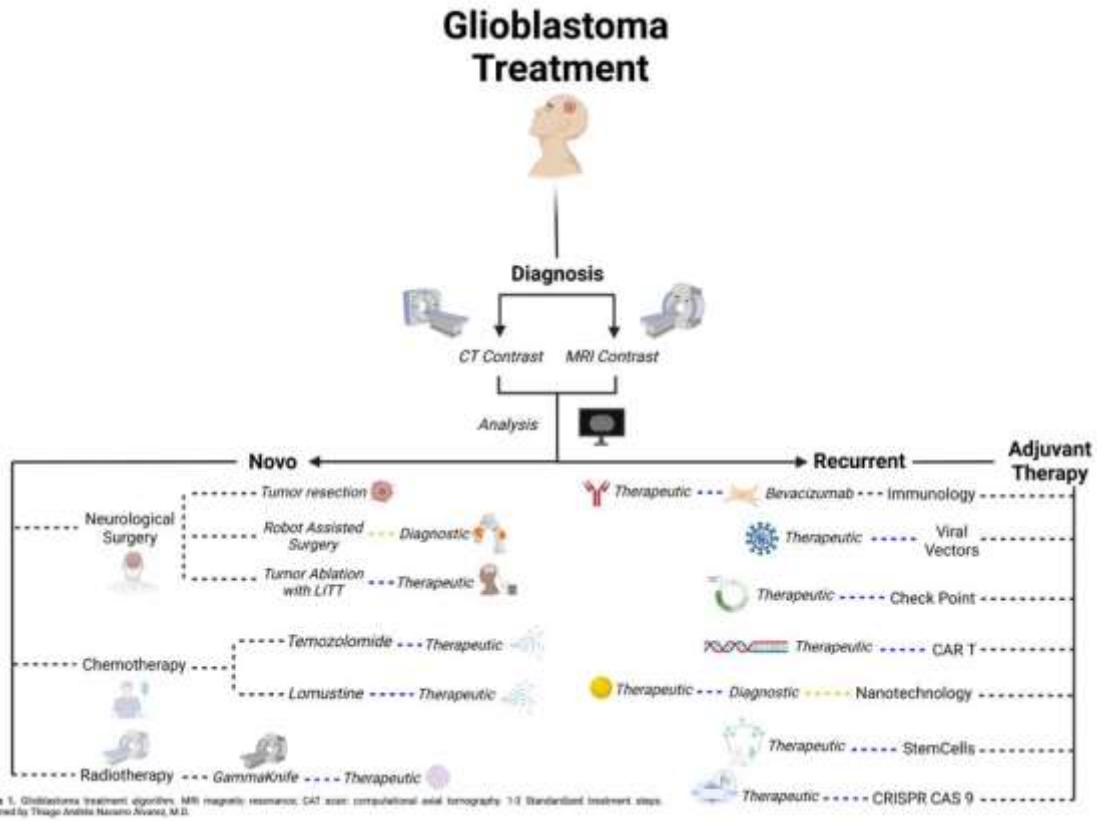

Figure 1. Glioblastoma treatment algorithm. MRI: magnetic resonance; CAT scan: Computational axial tomography; LITT: Laser interstitial thermal therapy.

Methods

A comprehensive review of the literature was carried out using the PubMed, Scopus, EBSCO, and Elsevier databases with the following search criteria: "Endovascular

Procedures"[Mesh], "Radiosurgery"[Mesh], "Radiotherapy"[Mesh], "Chemotherapy, Adjuvant"[Mesh], "Chemotherapy"[Text Word], "Immunomodulation"[Text Word], "Robotic Surgical Assistant" [Text Word], "Laser Interstitial Thermal Therapy" [Text Word], "Neurosurgery"[Mesh], "Neurosurgical Procedures"[Mesh], "Glioblastoma"[Mesh]. Two researchers selected the articles based on each article's individual merits. Full-text articles published between 2018 and 2023 were included. The titles and abstracts were first analyzed to exclude duplicated articles. Finally, the articles were selected based on the quality of the information they contained.

Results

Radiodiagnosis

The European Neuro-Oncology Association (EANO) established the diagnosis of brain tumors by simple cerebral magnetic resonance (MRI) and contracted with gadolinia in the pondered sequence FLAIR, T2, and T1 [11,12]. The use of infusion and positron emission tomography (PET/TC) of amino acids defines the critical points of metabolism in tumor tissue biopsies [11].

Neurological Surgery

The maximum safe macroscopic resection is generally the ideal therapeutic option in patients with malignant gliomas; the therapeutic advantages are related to both general survival and progression-free survival, as well as to reducing the mass effect and improving the neurological condition [13]. Currently, there are preoperative and intraoperative complements that guide surgical resections, which have the aim of preserving the integrity of the patient and impacting progression-free survival; these include craniotomy with an awake patient awake during which motor mapping and speech occur, neurosurgery assisted by a robot, and magnetic resonance surgery with fluorescence with 5-aminolevulinic acid (5-ALA), among others [13,14]. However, the indications of the different surgical alternatives depend on the diagnosis and/or therapeutic goal of the procedure.

Surgical resection: Craniotomy with the patient awake.

Awake craniotomy is a therapeutic neurosurgical technique used to resection brain tumors; it uses direct cortical and subcortical electrical stimulation and the active participation of the patient as a guide to surgical excision, maximizing the area of removal and reducing the secondary neurological lesions of the areas associated with speech, vision, and motor activity [15,16]. There is only limited evidence that this surgical technique in patients with GBM can produce acceptable rates of resection of supratentorial lesions and low rates of neurological deficits in the long term [15,17].

Laser interstitial thermal therapy (LITT)

Laser interstitial thermal therapy (LITT) is a thermocoagulative therapy applied in treating brain tumors. An important advance in its use has been the ability to send a laser signal to the region where the tumor is, hence causing tumor necrosis [18,19]. The technique employs high levels of laser-generated temperature that trigger an enzymatic response, which consists of protein denaturation and damage to the lipid membrane and, finally, results in coagulation necrosis; in addition, the surrounding brain tissue have been found to be protected [19].

LITT has been shown to be a suitable treatment for managing recurrent GBM2 and for tumors found in difficult areas to access [20,21]. However, Franca et al. [22] published a meta-analysis noting that there is still a need to establish a consensus on the precise indications for an intervention with LITT; their work highlighted that, in five specific situations, there is total agreement for using it: 1) recurrence after the combination of resection and maximum adjuvant therapy; 2) high surgical risk (because of basic diseases or by location); 3) safe trajectory for the use of LITT; 4) tumor volume of less than 3 cm^3; and 5) knowing the patient's preference for this procedure [22]. Some authors recommended that the maximum diameter for using LITT should be 3 cm to prevent the occurrence of malignant edema [23].
In terms of survival, this method has been shown to be comparable to other management schemes, with some advantages reported in different studies [19]: LITT is a minimally invasive procedure, and it can treat deep tumor lesions. It can also be used on multiple occasions for recurrent cases and does not require a pause in the patient's chemotherapy treatment. However, cases in which the use of LITT is not recommended include hypervascular lesions, multineoplasms, or giant tumors [24]. Studies have shown that the survival at six months of those patients treated with LITT procedures is similar to that of other treatments (75%), including in patients who are undergoing a craniotomy [25].

Robot-assisted neurosurgery

Minimally invasive surgery is being implemented gradually in all fields and specialties, thanks to the incorporation of robotic assistance. In the neurosurgery operating rooms in the United States, 40% of spine departments and 30% of skull departments have different robotic surgery systems [26].
The pioneering procedures in this field were biopsies using the PUMA560 System in the mid-1980s [27]. The robotic systems used today can be classified into three different types[28]: active, semiactive, and those controlled by the surgeon. Each one has managed to provide greater visualization of the surgical area, leading to higher levels of precision and reduced levels of surgeon fatigue and surgical complications [29].
Another important advantage of robotic assistance applied to neurosurgery is that it has allowed procedures to be performed in sites previously inaccessible [30], which has achieved, among other things, anatomical navigation functions that help in stabilizing the surgeon's actions. Another option is that the robot can perform the procedure while the surgeon controls it from a radiation-proof station [31,32]. Endovascular procedures have also benefited from the technological advances achieved with robotic assistants; they have managed to generate a catheter stabilization system that favors a decrease in movements and, therefore, in navigation and radiation exposure time [33]. Different authors have examined this factor because using robotic assistants requires learning time, and during the learning curve, procedures take more time [34].

Robotic stereotactic assistance

Technological developments have led to a progressive increase in robot-assisted surgical procedures, including the ROSA ONE Brain, which has an imaging device that optimizes navigation during the procedure and is increasingly being used to improve the precision and efficiency of interventions [35]. Its different uses in oncology are currently being explored because of its advantages in the ablation of epileptogenic foci and stereotactic electroencephalography [36–38].

This has all been thanks to current real-time navigation mechanisms and systems that have made possible the increase of the number of surgical procedures, the taking of biopsies and other medical applications for the treatment of deep brain lesions, or the management of high-grade tumor lesions [23,39] Moreover, the disadvantages that arise from robot assistance have been related to the extensive learning curve of surgeons and difficulties that arise for navigation if there is any movement on the operating table or by the patient [35].

Chemotherapy

Temozolomide

Currently, the United States Food and Drug Administration Agency (FDA) has approved temozolomide (TMZ) treatment for patients with a recent GBM diagnosis. This drug uses apoptosis, which induces alkylating agents in tumor cells that work by a specific action on DNA; the drug is administered orally and has been shown to have adequate CNS penetrance when it comes to passing through the blood brain barrier (BBB) [40,41].

Its effect depends on the normal expression of the methylation state of the O6 gene promoter-methylguanine-DNA-methyltransferase (MGMT), which is associated with the repairer enzyme effect on DNA and removal of alkyl groups that prevent apoptosis of noncancerous cells and decrease the toxic effects of treatment; therefore, its expression has been established as a relevant prognostic biomarker and predictor of chemotherapy response. However, 55% of patients are estimated to express an abnormal methylation phenotype [40,42–44].

Stupp et al. (2005) established a treatment protocol consisting of six cycles of TMZ concomitant with radiation therapy, which has been found to ben beneficial for general survival and clinical evolution in the early stages of GBM diagnosis [45,46]. Unfortunately, the average five-year survival rate is estimated as being less than 5%. This scheme has a favorable safety profile, with immunosuppressive impacts on bone marrow mainly related to thrombocytopenia and secondary liver conditions [11,41].

Lomustine

One of the most described therapeutic alternatives for treating recurrent GBM is lomustine, a DNA and RNA alkylating agent lipid-soluble capable of penetrating the BBB [47]. It is indicated on monotherapy or combination therapy with procarbazine and vincristine; however, clinical response rates of between 10% and 20% have been estimated, with an average progression-free survival of two to six months in oral administrations at intervals of six to eight weeks, with expected side effects of late myelosuppression, here mainly thrombocytopenia [47–49].

Radiosurgery

Single fraction radiosurgery (SRS) is an approved therapeutic alternative for the treatment of functional disorders and intracranial tumor lesions of benign and malignant origin that require the use of intraprocedural diagnostic images for advanced brain mapping and the directed administration of a high-dose ionizing beam of radiation, with the aim of destroying malignant cells and not the surrounding healthy tissue. Nevertheless, several studies documented local failures and complications related to postoperative radiosurgery, including radiation necrosis and leptomeningeal disease [50–52].

Because of the promising results of preclinical studies on improvements in antitumor immunological response, the Mayo Clinic is currently carrying out the NeoGlioma study

(NCT05030298) to implement a radiosurgery scheme after surgical resection in patients with high-grade gliomas [52].

Adjuvant Therapeutics

Effective therapeutic alternatives for patients with recurrent GBM or relapses are a challenge for modern medicine, which has given rise to the generation of nonstandardized adjuvant therapeutic options, among which systemic therapy, immunotherapies, radiation therapy, and molecular therapies have been highlighted [13,53].

Targeted molecular therapies: Bevacizumab

Based on clinical and preclinical results, the FDA approved the use of bevacizumab—a humanized monoclonal antibody that works against the vascular endothelial growth factor (VEGF)—in patients diagnosed with recurrent GBM and who are characterized by the overexpression of VEGF, high levels of neoangiogenesis, and interruption of the hematoencephalic barrier (BBB) [4,14,53]. Therefore, it is considered the antiangiogenic drug of choice, with potential benefits associated with reducing the surrounding brain edema and steroid-saving effect [54].

The RTOG 0825 trial reported minimal improvement in general survival without statistically significant differences in monotherapy. Life expectancy increased 5.1 months when patients were given lomustine (EORTC 26101) [55]. On the other hand, joint administrations with irinotecan have shown an improvement in progression-free survival compared with other schemes. In combination with chemoradiation therapy, general survival has been shown to improve, and in combined radiation therapy, it delays tumor progression compared with single sessions of hypofractioned radiation therapy [5,55].

However, despite the proper general tolerance and documented benefits of the quality and reduction of steroid use in the long term, significant side effects have been described, including nephrotic syndrome, venous and arterial thrombosis, bleeding, heart failure, and delays in wound healing [54,55].

Immunotherapy

Currently, immunotherapy represents an innovative and relevant field of study focused on the regulation of the immunosuppressive and protumor effects generated by the tumor growth of glial cells. This vicious circle also conditions the antitumor pharmacological response because of the expression of immunosuppressive factors, such as indolamine 2,3-dioxygenase (IDO), interleukin 10 (IL-10), programmed cell death protein 1 ligand (PD-L1), transforming growth factor β (TGF-β), and the inhibitors of proliferation and activation of T lymphocytes, among others. The inhibition of these factors will result in a promising treatment alternative for patients with GBM, with the additional advantage of a broad decrease in adverse effects [41,56,57]. The main immunotherapeutic agents are described below.

CAR-T therapy

Technological advances have resulted in the advent of genetic engineering that enables the transfer of synthetic proteins to autologous T cells by plasmapheresis using RNA or viral vectors that induce the presentation of chimeric antigen receptors (CAR-T); this can establish immune complexes with tumor cells and induce a lasting immunological response that is independent of the human leukocyte antigen [41,58].

CAR-T is composed of three domains: 1) the ectodominium or extracellular domain with a variable fragment of a single chain (scFv) detects antigens on the tumor's surface, 2) the transmembrane domain facilitates the transmission of activation signals from the CD3 domain, and 3) the endodominium or intracellular domain senses a second costimulating signal for the selective proliferation of lymphocytes, among which OX40, CD28, CD27, and CD137 have been highlighted [56].
There are promising preclinical trials in rodent models that have focused on the intracranial administration of CAR-T EGFRvIII, CD70, HER2, and L13Rα2 cells, here using the CD137 costimulator as a way to increase the efficiency of the inflammatory response and general survival. Currently, the FDA has only authorized the administration of two types of therapy in patients with refractory hematological malignancies; these therapies have shown favorable results [56,58].

Checkpoint
Current evidence has demonstrated the establishment of a variant immunosuppressive tumor microenvironment that can facilitate the neoplastic growth of gliomas through the infiltration of malignant cells into the bloodstream, which uses mechanisms to regulate the T-cell response to cancer cells, generating a state of tolerance and immune evasion [56,59]. One of these mechanisms was recently identified and evaluated, in which the immune checkpoints were found to mediate with the inhibitory response on T cells and allowed for enhancing immunosuppression state. Therefore, immunotherapy seeks to generate synthetic molecular ligands that may inhibit glioma-specific checkpoints such as CTLA-4, LAG-3, IDO, TIM-3, and PD-1 [56,59].

Viral therapy
Immunotherapy is the results of genetically modifying a virus with the goal of detecting and eliminating cancer cells through oncolysis, with the activation of the immunological response mediated by new viral particles. Approved viral therapies for metastatic melanomas and head and neck neoplasms have been documented with favorable results; however, there are no standardized protocols for the treatment of gliomas with virus oncolytics, and clinical studies for viral gliomas in animals are being developed from adenovirus (DNX-2401 and ONYX), herpes virus simple (R-115, G207, and M032), and poliovirus, all of which have shown promising results [56,60].

Nanotechnology
Nanotechnology is a promising research field for the treatment of CNS neoplasms such as GBM. In this area, there are two goals: 1) developing the mechanisms of BBB disruption by using ultrasound or magnetic fields to facilitate the passage of nanoparticles and/or nanoparticles and 2) the creation of nanomaterials composed of dendrimers, liposomes, supermagnetic nanoparticles, polymeric nanoparticles, carbon nanomaterials, and so forth. These particles can function as the carriers of the transmembrane transportation of chemotherapeutic molecules, such as cisplatin, paclitaxel, and temozolomide. Through the BBB, deposits are created in tumor tissue by increasing its bioavailability and reducing the risk of systemic side effects and toxicity. This has been supported by the effect of permeability and improved retention; however, until now, the nanoparticles has been inefficient and has not generated the complete deposits needed to eliminate malignant lesions in humans [61,62].

Stem cells

Malignant tumor lesions are capable of expressing small populations of cancer stem cells related to the processes of therapeutic and relapse resistance. In some tumors derived from the cells of the glia, fundamental glioma stem cells (GSC) have been recognized in the process of establishing the tumor microenvironment by cellular proliferation, angiogenesis, and therapeutic resistance, which facilitate maintaining the secondary immunosuppressive response. GSC preferably establish themselves in the perivascular and perinecrotic areas of the tumor, where they express highly invasive protumoral molecular markers from hypoxia; GSC has been identified in patients with a wild-type GBM of isocitrate dehydrogenase (IDH) [4,63,64].

CRISPR CAS 9

The clustered regularly interspaced short palindromic repeats system (CRISPR) is a state-of-the-art technology designed for the genomic editing of several types of cancers, including GBM. Cas9 is a DNA endonuclease enzyme directed by a guide RNA that is capable of breaking the DNA double strand, leading to genomic editing [65,66]. This situation has allowed for the development of gene techniques aimed at controlling the processes of cell proliferation and angiogenesis, which leads to a decrease in the invasiveness of tumor cells, thus facilitating the identification of therapeutic targets. However, this technique still requires further work because the heterogeneous nature of tumor cells and the in vivo effects of these therapies have led to unsatisfactory results and possible undesirable gene mutations [65,66].

Conclusion

Glioblastoma is the most frequent and lethal primary tumor of the CNS. It is generally associated with a poor prognosis in both the short and medium terms. The most common treatment is surgery associated with chemotherapy sessions with drugs such as temozolomide and radiotherapy; this treatment scheme has shown fewer complications.

However, recent evidence of alternative management schemes, such as LITT thermocoagulative therapy and robot-supported surgery, allows for minimally invasive procedures and reduces human error. Furthermore, in patients with recurrent neoplasms, the use of adjuvant therapies, such as bevacizumab and other immunotherapy schemes, is indicated, which are emerging as a source of research for the development of individualized therapies with a lower risk of failure.

The different alternatives of management have generated scarce results on the evolution of the disease, the clinical prognosis continues to be unfavorable, and survival does not exceed 18 months yet. Therefore, it is necessary to continue with technological and scientific advances to improve the understanding of the disease to enhance the various current therapeutic options and develop new options that allow for the extension of survival together with quality of life.

The inclusion of clinical simulation processes within technological development complexes involving interdisciplinary teams will enable better health outcomes in the future through scientific innovations that enhance patients' hope and quality of life[67].

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