State-of-the-Art of Glioblastoma Treatment

Subjects: Oncology

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Glioblastoma is the most frequent and lethal primary tumor of the central nervous system. Through many years, research has brought various advances in glioblastoma treatment. Glioblastoma management is based on maximal safe surgical resection, radiotherapy, and chemotherapy with temozolomide. Bevacizumab has been added to the treatment arsenal for the recurrent scenario. Despite the great efforts in therapeutic research, glioblastoma management has suffered minimal changes, and the prognosis remains poor. Combined therapeutic strategies and delivery methods, including immunotherapy, synthetic molecules, natural compounds, and glioblastoma stem cell inhibition, may potentiate the standard of care therapy and represent the next step in glioblastoma management research.

Keywords: glioblastoma ; Historical ; Pathophysiology ; State-of-the-Art: ; Glioblastoma multiforme ; GBM ; Radiotherapy ; Neurosurgery

1. Introduction

Glioblastoma (GB) is one of the most lethal malignancies in the human body and the most common primary brain tumor, representing a significant challenge in neuro-oncology. Unfortunately, since Roger Stupp et al. described the current standard treatment more than fifteen years ago, the prognosis remains poor. The long-term survival has only been slightly modified, despite incessant efforts in basic, translational and clinical research [1][2].

The Stupp protocol includes maximally safe surgical resection, followed by involved-field radiotherapy (RT) (60 Gy in 2.0 Gy fractions on weekdays) over a six-week period, (42 days) with daily concomitant temozolomide (TMZ) (75 mg/m^2) chemotherapy, followed by six cycles of adjuvant TMZ maintenance (150–200 mg/m^2), administered for five days every 28 days [1][3].

Even though therapy is always followed by tumor recurrence and progression, recent advances in multimodality therapy have improved the median survival to approximately 15 months (14–21 months), the progression-free survival (PFS) to 10 + 1 months before recurrence, the one-year survival rate to 41.4%, and a five-year survival rate to 6.8% [1]. On one side, there are well-established negative prognostic factors, such as advanced age, poor performance status, and incomplete extent of resection. On the other side, molecular features, such as isocitrate dehydrogenase 1 (IDH-1), IDH-2 mutation, and MGMT methylation confer a favorable prognosis [2][3].

Multiple treatment options for recurrences have evolved in the previous decade, including systemic therapy, such as bevacizumab (BEV), nitrosoureas, immunotherapy, such as vaccine therapy, checkpoint inhibitors, and CAR T cell therapy, or oncolytic viruses, among others. In some cases, first-line approaches can be employed again in recurrences. There is not a well-defined standard of care for tumor recurrences, due to the lack of evidence to improve overall survival (OS) [3][4].

2. Historical Perspective

The neuropathologists Percival Bailey and Harvey Cushing were responsible for the modern classification of gliomas in 1926, nearly 100 years after gliomas were first described and more than 50 years after Virchow proposed the first classification. Due to the multiform appearance of cells within the same tissue samples, Bailey and Cushing named the most clinically malignant and histologically unusual form of glioma Spongioblastoma Multiforme [5][6].

Due to the unusual and polymorphic monstrous cells, which exhibit no resemblance to healthy glial or even other glioma cells, they were convinced that this tumor type had a different biological genesis than other gliomas. Although astrocytoma

arises from astrocytic glia and their neoplastic cells bear some similarities, spongioblastoma multiforme was considered a different type of tumor, according to their classification. The word spongioblastoma was eventually ruled out in favor of glioblastoma, establishing the common origin of astrocytoma and glioblastoma multiforme [5][6].

Since the description of GB, many treatment approaches have been tried to fight this cancer. As a result, a lot of knowledge and advances have been achieved; nevertheless, patients with glioblastoma do not yet have a favorable prognosis. An important landmark in the timeline of GB treatment occurred in 2005 when Stupp et al. published the results from their GB treatment protocol, based on surgical resection, radiotherapy, and temozolomide. Nowadays, it is still recognized as the gold standard for this type of tumor.

Before 2005, surgical resection was the gold standard for patients diagnosed with glioblastoma, with a median survival time of 13 months for those with 98% of tumor resection [7]. Then, radiotherapy was added to treatment guidelines, showing a discreet benefit for patients with primary and recurrent tumors [8]. Last, chemotherapy (CT) was introduced to the GB treatment scheme with temozolomide, which was first used in cycles for recurrent tumors [9]. All these advances provide a slightly better prognosis for patients with GB.

3. Glioblastoma Pathophysiology

Mutations in IDH1 and IDH2 are among the most well-studied metabolic disturbances in gliomas, including GB. IDH1 is a citric acid (Krebs) cycle enzyme that converts isocitrate to a-ketoglutarate (a-KG) and is essential to produce adenosine triphosphate (ATP) during cellular energy production. During the Krebs cycle, isocitrate, produced by the isomerization of citrate, is oxidized and decarboxylated. The IDH enzyme surrounds the isocitrate in its active site by amino acids, such as arginine, tyrosine, and aspartic acid. During the first stage of the reaction, carbon #2 of the isocitrate is oxidized to form oxalosuccinate. The alcohol group on this carbon is deprotonated, electrons flow to the carbon forming a ketone group and a hydride ion is removed using NAD+/NADP+ as an electron-accepting cofactor. Then, in the second stage, the oxalosuccinate is decarboxylated. A nearby tyrosine residue deprotonates oxygen from the carboxyl group, and electrons flow to carbon #2. Carbon dioxide leaves the beta carbon of the isocitrate, electrons flow to the oxygen of the ketone group, and the latter becomes negatively charged. Finally, a double bond is formed between the alpha and beta carbons. In the third stage, the double bond between carbon #2 and #3 is saturated. A lysine residue deprotonates the oxygen of the alpha carbon regenerating the ketone bond and forming a single bond between the alpha and beta carbons by taking a proton from a nearby tyrosine residue [10][11][12].

Gliomas are known to have recurrent hotspot missense mutations in IDH1 and IDH2. IDH1 (R132) and IDH2 (R132) both have mutations at a single amino acid residue (R140). Tumors have only one mutant copy of each gene. According to groundbreaking investigations, the tumor-derived IDH mutations are neo-morphic, meaning they gain new enzymatic activity and can convert -KG to (R)-2-hydroxyglutarate (2HG). IDH1 mutations produce a distinct metabolite, 2-hydroxyglutarate (2HG), promoting a hypermethylation phenotype in gliomas [10][11]. The mutant variant of IDH1 has been found to interact with the IDH-wildtype enzyme, reducing its activity. Gain-of-function mutations in IDH1 result in the synthesis of the oncometabolite 2HG from a-KG. As a result, 2HG levels are higher in IDH1 or IDH2 mutant gliomas than in IDH wild-type tumors [12][13].

In gliomas, the hypoxia-inducible factor 1-alpha (HIF-1a) is a significant pro-angiogenic and pro-glycolysis transcription factor that is increased in IDH1 mutant GB cells. This transcription factor targets GLUT1, VEGF, and PDK1 genes. Prolyl hydroxylase (PHD) enzymes, which inhibit HIF-1a, are inhibited by IDH1 mutations and 2HG generation [12][14].

The occurrence of a CpG island hyper-methylator phenotype (CIMP) is a second change linked to IDH1 mutations, which displays distinct CpG island methylation at a more significant number of locations than non-IDH1 mutants and primary GB, according to a genome-wide methylation profile investigation in gliomas. In addition, the induction of mutant IDH1 into human astrocytes produces functional changes, and, in particular, histone markers by impairing histone demethylation and inducing DNA hypermethylation. As a result, in gliomas, the IDH1 mutation has an important role in hypermethylation [12][15].

A sequence of human tumors for IDH1 or IDH2 mutations, or monoclonal antibodies against the most common IDH1 mutation (R132H), allows for immunohistochemical analysis of low-grade gliomas and GBMs. Now, it is possible to use MRI spectrometry to detect the IDH mutant's oncometabolite, 2HG, which may allow a noninvasive classification of the grade and subtype of glioma. This technique may be used to evaluate responses of potential treatments against IDH mutant tumors [16].

The O6-methylguanine-DNA methyltransferase (MGMT) gene encodes for a DNA repair protein that removes alkyl groups from the O6 position of guanine, which is a key location for DNA alkylation. Chemotherapy-induced alkylation causes cytotoxicity and apoptosis at this location. Tumor cells that overexpress the MGMT repair protein could be capable of blocking the therapeutic effects of alkylating drugs. In over 40% of primary glioblastomas, and over 70% of secondary glioblastomas, MGMT is epigenetically inactivated by hypermethylation of the 5'-CpG island. CpG islands are genomic areas with a higher than usual frequency of CG dinucleotides (CpG sites), which are involved in gene transcription modulation [17].

CpG islands, such as the one linked to the MGMT gene, frequently span the transcription start site of genes and contain essential transcription factor binding sites. Aberrant methylation of CpG islands can cause gene transcription to be disrupted, resulting in reduced, or even complete loss of, gene product expression. However, the methylation patterns of the MGMT promoter in malignant gliomas differ widely, and it is unclear which exact CpG sites or combinations of CpG sites must be methylated to silence the gene and benefit from alkylating drug therapy [17].

The exact origin of a GB is rarely identified, but it is suggested to derive from neural stem cells (NSCs) or glial precursor cells, which have the ability to infiltrate brain tissue and cause endothelial necrosis, creating the typical histopathological inflammatory pattern. The aggressive behavior of GB is likely determined by a small subpopulation of cancer cells named glioblastoma stem cells (GSCs), which have pluripotential and self-renewal capacity. These characteristics protect GSCs from chemotherapy- and radiotherapy-induced damage. Targeting stem cells or inducing differentiation are innovative therapeutic strategies covered by new synthetic molecules and some natural compounds described later. Alternative drug delivery systems through stem cell mechanisms are already being tested in several preclinical trials [18][19].

4. State-of-the-Art: Surgery, Tumor Treating Fields, Radiotherapy, Chemotherapy and Bevacizumab

4.1. Safe Maximum Resection

Many years before the Stupp et al. trial was published in 2005, maximal safe resection surgery was the initial technique in the gold standard of treatment [1]. The surgery's primary treatment goal is to achieve a gross total resection (GTR) as safely as feasible without risking the patient's functional state. Tumor volume reduction, histological diagnosis, and tumor genotyping are all possible with the surgical approach, all of which are essential factors in selecting the following stages in treatment. A stereotactic or open biopsy is advised if surgical resection is not an option [2][20][21].

Full resection involves removing the entire contrast-enhancing tumor in the T1 gadolinium weighted image. Full resection has been associated with a higher chance of survival and no progression than partial resection or biopsy. Several surgical tools have been developed to assist in achieving a maximal resection of the tumoral tissue while trying to avoid, as much as possible, the neurological deficits related to the procedure. Such tools include surgical navigation systems with functional MRI (fMRI), functional monitoring, and fluorescence-based visualization of tumor tissue with 5-aminolevulinic acid (5-ALA) or fluorescein. In addition, when a tumor involves eloquent areas, functional tools such as brain mapping in awake patients, evoked potentials, or electromyography have shown beneficial results in long-term neurological functional outcomes [21][22][23].

ALA is a body-produced metabolite in the biosynthesis pathway that is given as a 20 mg/kg body-weight oral solution. This molecule is rapidly absorbed and eliminated from plasma within 2 h of treatment, due to its small size. After 6 to 8 h, a peak fluorescence can be expected, with fluorescence being evident after 3 h. Gliomas selectively take up ALA and convert it to protoporphyrin IX (PPIX) via enzymes in this pathway. Many investigations have shown that ALA-induced PPIX has a high selectivity, although normal brain tissue does not develop PPIX in response to ALA exposure [24][25]. All of the main current surgical microscopes have adjuncts that can visualize PPIX. Filtered xenon light with a wavelength of 375 to 440 nm and an emission filter that allows viewing red fluorescence with a peak at 635 and 704 nm are required to visualize PPIX fluorescence. The filters are also designed to let some of the excitation light and green autofluorescence emitted by the tissue to pass through, allowing background discrimination and fluorescence surgery over more extended periods of time [24][25][26][27].

Fluorescein was the first agent to be utilized intraoperatively for better tumor detection and identification. It is administered intravenously in doses ranging from 3 mg to 20 mg/kg during induction of anesthesia, prior to dural opening, or acutely, during resection, using either dedicated microscopes or microscopes without any specific adjuncts for fluorescence visualization. Due to the extra time between injection and resection, fluorescein is eliminated from the dura and venous

system, and is only retained in locations where the blood-brain barrier has been damaged, allowing for tumor delimitation [24][26][28].

It is important to remember that gliomas are not cured by surgery alone. Nowadays, even though the extent of resection is a prognostic factor, and efforts at obtaining complete resections are always justified, the priority is to prevent neurological deficits caused by surgery. Neurological deficits arising from surgery cause reduced independence and quality of life, which lead to increased complications that may even impede the following steps in the standard management, such as radiotherapy or chemotherapy, which have more impact in the final overcome than the extent of resection [22][23][26].

All patients have a different clinical presentation of their disease, and some of them may have some negative prognostic factors that surgical procedures can modify. For example, the initial prognosis for multicentric lesions or multifocal tumors is poor, but surgical resection management improves it. Another significant poor prognostic factor is when a GTR is not accomplished and significant post-surgical residual tumor volumes remain [3][23].

Recent research suggests that the tumor's biological features may influence its resectability. Some uncontrolled retrospective studies observed that the rate of GTR was higher in IDH-mutant tumors than in IDH-wildtype tumors. Less malignant brain tumors may be more resectable than tumors with more aggressive biological characteristics. This consideration does not discourage the efforts to achieve gross total resection when feasible. If possible, GTR is advised in recurrent cases with a time interval of >6 months since the first surgery, especially in younger patients with a good clinical state [2][27][29].

Awake Craniotomy

Awake craniotomy (AC) with intraoperative cortical electrodes for motor and speech monitoring has obtained outstanding results. It is the current gold standard technique for diffuse brain tumor resections, due to its capacity to identify and preserve cortical and subcortical functional areas. The main aim of AC is to preserve motor and speech functions and achieve a complete resection of the tumor [22].

For a successful outcome, suitable patients must be chosen. Uncontrolled chronic cough, hemiplegia with motor function <2 on the Daniel's scale, severe dysphasia, and big tumors with mass effect resulting in >2 cm of midline shift are all absolute contraindications for awake craniotomy [27]. However, individualization of the patient is essential, considering that adaptation is possible in some instances [22][29]

During AC, different anesthetic approaches are employed, including conscious sedation (CS) and the asleep-awake-asleep procedure (AAA). Conscious sedation entails supplementary oxygen, spontaneous ventilation, and modest doses of sedative medications. Dexmedetomidine has been demonstrated to decrease the number of sedatives and opioids required. It has strong effectiveness and a strong safety record [23][27][30][31].

The AAA technique uses general anesthesia before and after cortical mapping and functional testing. Drug infusion is interrupted 15 min before the functional testing, and ventilatory support is removed when the patient obeys commands [22]. When the neurological examination is completed, anesthesia is induced, and ventilatory support is restarted. The primary goals of this technique are to maintain the pre-awake state, shield the patient from discomfort, reduce brain swelling through hyperventilation, and restrict patient movement during operation [2][22][30][31].

Intraoperative magnetic resonance imaging (I-MRI) is a technique that has been used in addition to mapping during awake craniotomy. This tool provides real-time intraoperative MRI images that detect the tumor and its remnants, which allows better precision, enabling consideration of the changes in the brain anatomy during surgery. The combination of both techniques enables maximum resection while minimizing neurological deterioration [22][31].

4.2. Radiotherapy

Radiotherapy (RT) has been a cornerstone in the treatment of GB for more than fifteen years. The main goal of RT is to improve local control without inducing neurotoxicity. Current guidelines recommend 60 Gy administered in 2.0 Gy fractions on weekdays for six weeks for first-time treated GB (from Monday to Friday), starting 3–5 weeks after surgery. RT usually starts 3–5 weeks after surgery. When CT/RT is received >5 weeks after surgery, a reduction of 3 months in PFS has been observed in a retrospective study. The inter-lapse between surgery and RT/CT is inversely related to PFS and OS. However, tumor recurrence and progression virtually always occur after treatment [2][21][32].

A planned goal volume should include the gross tumor volume (GTV = area of surgical bed + residual tumor area in T1WI, T2WI/FLAIR sequences) and a clinical target volume that involves a 1–2 cm margin to account for microscopic invasion.

Also, a 0.3–0.5 cm margin is added, considering the uncertainties that may coexist. The administration dosages should be 50–60 Gy in 1.8–2 Gy daily portions over six weeks. Other radiotherapy doses, schemes, and ionizing radiation techniques have been tested for primary treated GB without conclusive results [32].

According to the Karnofsky performance scale (KPS) index, radiotherapy doses can be adjusted. When compared to supportive treatment alone, a dose of 50 Gy in 1.8 Gy fractions provided an OS benefit for elderly (>70 years) patients with a good functional status (KPS > 70) (29.1 weeks vs. 16.9 weeks). A hypo-fractionated regimen of 40 Gy in 15 fractions of 2.67 Gy over three weeks has shown equivalent survival outcomes to standard dosages in patients with poor functional conditions (KPS < 70) [2][32].

Adaptive RT is gaining popularity in the treatment of GB. It consists of the application of RT and a subsequent evaluation of changes in tumor size and form by sequential CT/MRI scans. The dosages are modified based on the new circumstance, usually lowering complications and enhancing the long-term quality of life by minimizing radiation to adjacent normal tissues. Studies have shown adaptive RT to improve irradiation efficacy in the target volume and lower the dosage received by organs at risk while also increasing local control, OS, and PFS. However, further research is needed to determine the benefits of adaptive RT [2][3][23][32].

Recently, studies evaluating the combination of hypo-fractionated RT and concurrent TMZ showed a better OS (9.3 months) than radiation alone (7.6 months) (HR, 0.67; 95 percent CI, 0.56–0.80 [$p < 0.001$]) with no differences in quality of life. However, these trials did not compare the groups to standard-of-care (SOC) RT + TMZ. Further studies comparing hypo-fractionated RT + SOC should be conducted [2][32][33].

For recurrences, radiotherapy has been studied as a potential treatment alternative, particularly for younger patients with good performance status. However, several radio-resistance mechanisms, developed on the first RT course, have put the supposed benefits of re-irradiation in question. For recurrences, various ionizing radiation treatments have been investigated, including highly conformal radiation techniques, such as intensity-modulated RT, proton or heavy ion irradiation, stereotactic radiotherapy (SRT), radiosurgery (SRS), and hypo- and hyper-fractioned regimens. Nevertheless, more randomized control trials (RCTs) are required to determine these approaches' tolerability, safety, and efficacy compared to standard radiotherapy [4][33]. Recently, new synthetic molecules and natural compounds have demonstrated radiosensitizer properties in pre-clinical trials. Results are discussed later in the text.

In GB recurrence, the efficacy and safety of SRS and SRT have been investigated. In a trial using SRS, patients who received a median dose of 24 Gy in four fractions had a median OS of 14.6 months after treatment, with no toxicities registered. Safety and outcome improvement has been reported in retrospective evidence about SRS and short courses of hypo-fractionated SRT in GB recurrences. An ongoing prospective phase II study (NCT04197492) is investigating the value of hypo-fractionated SRS in recurrent HGG [2][32][33].

About the efficacy of gamma knife radiosurgery (GKRS) in high-grade glioma (HHG) recurrences, a study observed a median OS of 13 months and a survival rate of 51.4% at 1-year, 10% at 2-years, and 2.9% at 5-years, which can represent a different area of interest [32].

A combination of RT and systemic treatments, such as bevacizumab, has already been investigated in GB recurrence. After delivering a combined therapy of BEV+ RT/TMZ to patients in phase III studies, the results showed only a PFS improvement with no changes in OS. Recent research has found similar findings in PFS with a tolerable toxicity profile [32]. Kulinich, on the other hand, conducted a comprehensive evaluation of data from patients with recurrent GB who had been treated with SOC therapy and then retreated with the BEV+ RT combination as a second therapy. After multivariate analysis, they discovered a slight improvement in OS but no meaningful advantage in PFS. Furthermore, the data revealed that patients who took BEV had a much lower rate of radio-necrosis [2][32][33].

The combined therapy of BEV + RT is an optimistic regimen for the GB recurrence instance, which has shown acceptable safety profiles, improvement in OS, and potential reduction of radio-necrosis. Nevertheless, the inconsistency between trial results exhibits the need for further investigation that includes analysis of the possible patient and tumor characteristics involved in the outcome [2][32][34].

Several ionizing radiation treatments and regimens have been examined, particularly in the GB recurrence scenario. Nonetheless, current guidelines only agree on SOC conventional radiotherapy for first-time GB patients. Although the significance of re-irradiation in recurrent GB is unclear, research into combined BEV+ RT, SRS, SRT, and GKRS seems promising [2][32][34].

Aside from the well-known effects of radiation on tumor cells, DNA alkylation, endothelial damage, and the creation of free radicals, the effects on cell membrane proteins are crucial. Proteoglycans (PGs), for example, are implicated in initial glioblastoma development and contribute to cancer stem cell (CSC) treatment resistance and GBM recurrence development. Radiotherapy reduces brevican and neurocan concentrations in cerebrospinal fluid at 12-months following irradiation [35]. Hyaluronic acid (HA) is a PG component of any tissue but plays an especially critical role in the brain. It comprises a significant component of intercellular space, is involved in GB pathogenesis, and is damaged by radiotherapy. RT causes a considerable rise in HA content. In addition, HA interaction with the CD44 receptor induces a mesenchymal shift in GBM cells. An increase in HA content on the tumor tissue affects the microenvironment, providing pro-invasive extracellular signaling [35].

Other essential effects induced by RT are early metabolic responses in the tumor and the adjacent tissue during the first week of RT. Glutamate is a non-essential amino acid and a primary excitatory neurotransmitter. It has been linked to the invasive process and a high frequency of seizures in patients with HGG. Glioma cells have been shown to release a high glutamate concentration, causing widespread excitotoxic death in normal neurons, whereas normal astrocytes remove glutamate from the extracellular space. This process promotes tumor growth and invasiveness. Glutamate levels rise after radiation and have been proposed as a marker for ischemia and traumatic brain injury. The radiation-induced glutamate increase could be due to a release from the tumor or astrocytic cells injured by radiation [36].

Myo-inositol is a crucial intracellular and second messenger molecule and is involved in signaling, and is abundant in brain adjacent tissue (BAT). Myo-inositol promotes the generation of phosphatidylinositol, which is then used to produce diacylglycerol and inositol 1,4,5-trisphosphate (IP3). Protein kinase C and a cascade of proteolytic enzymes, including matrix metalloproteases, are activated as a result of the diacylglycerol, which plays an essential role in tumor invasion. In both the tumor and the BAT, there is a rise in inositol. A variety of signaling and secondary messenger molecules are based on inositol and Myo-inositol. Ca^{2+} is released when the IP3 receptor is stimulated by IP3, rendering the cells more sensitive to apoptotic triggers. The inositol rise is caused by a decrease in the synthesis of IP3, which leads to decreased sensitivity to apoptotic stimuli, enhancing glioma cell resistance to radiation-induced apoptosis [36].

S-methyl-L-cysteine levels are more significant in tumors than in BAT. S-methyl-L-cysteine is the end product of a methylated-DNA-cysteine S-methyltransferase mediated demethylation process of DNA containing methylguanine. S-methyl-Lcysteine levels in tumor tissue drop after RT, suggesting that the treatment interferes with the methylated-DNA-cysteine S-methyltransferase-mediated demethylation process [36].

4.3. Chemotherapy: Temozolomide (TMZ)

Temozolomide, an oral DNA alkylating drug that penetrates the blood-brain barrier, is the current first-line, and most used, systemic therapy for GB. In its passage into the cytoplasm, TMZ undergoes spontaneous hydrolysis to form monomethyl triazene 5-(3-methyltriazene-1-yl)-imidazole-4-carboxamide (MTIC). This compound is then hydrolyzed to form the final cation methyldiazonium. This active cation adds a methyl group to purines and pyrimidines in DNA, specifically in the N^7 position of guanine (70%), guanine rich sites, and to a lesser extent in N^3 adenine (9%), and O^6 guanine residues (6%). These methylation modifications result in damage to cells, apoptosis, and cell cycle arrest at the G2/M phase [37]. During concurrent RT, the daily optimum dose is 75 mg/m^2 for a six-week period (42 days), followed by six cycles of maintenance of 150–200 mg/m2 for five days every 28 days. In patients with poor performance status (KPS < 70), it is suggested to administer TMZ alone at 150–200 mg/m^2 for five days every 28 days after surgery. For newly diagnosed GB, there is no evidence of benefit from different TMZ doses or treatment strategies [2][4].

Patients that will benefit from the treatment are those whose tumors have aberrant CpG methylation of the promoter area of the DNA repair enzyme MGMT gene. This methylation limits the transcription of an enzyme involved in DNA reparation following the genotoxic effects of alkylating chemotherapy. Approximately 55% of GB patients are resistant to TMZ because of their MGMT DNA repair system. MGMT transfers the methyl group from guanine, thereby repairing damaged DNA and counteracting the cytotoxic effects of TMZ on tumor cells [37]. Studies have indicated that patients with MGMT methylated tumors have a better prognosis, with a median 2-year survival rate of 46%, implying that TMZ is exclusively active in this kind of GB, with only a minor effect on MGMT unmethylated tumors [20][21].

Unfortunately, evidence indicates an evolution to recurrence in almost every patient at six months within the standard treatment. In this instance, no standard treatment is established, but the most commonly employed systemic therapies are alkylating agents like TMZ rechallenge or nitrosoureas, such as lomustine and carmustine. The MGMT methylation status plays the same role as in primary management. Low-grade evidence studies on individual chemotherapy indicate minimal changes in OS and greater toxicity with other regimens [4][23].

Myelosuppression, particularly thrombocytopenia, neutropenia, nausea, and hepatic damage, are the most common side effects of alkylating drug treatment. Even though adverse effects are typical during the adjuvant phase, the hepatic function should be examined regularly in patients receiving TMZ [2][3]. The use of nanotechnology to increase chemotherapy administration to the CNS via the blood-brain barrier (BBB) is a promising alternative that is still in research [20][21].

Nitrosoureas, such as lomustine and nomustine, are oral alkylating drugs that have been used to treat GB. Their mechanisms consist in alkylate DNA and RNA, as well as cross-link DNA, acting both in and out of the cell cycle. The production of O6 -chloroethylguanine, which can be reversed by MGMT, is one of the most important lesions generated by lomustine [38]. By carboxylation of amino acids, such as lysine or arginine, lomustine may impede enzymatic processes, leading to cell death through TRC8-mediated degradation targeting heme oxygenase-1 [39]. However, the clinical relevance of this action is uncertain. As a result of its lipo-solubility, it easily crosses the BBB, making it a viable candidate for treating intrinsic brain cancers [38][40].

Lomustine has recently been tested in combination with TMZ to observe a possible booster effect of TMZ on lomustine efficacy to deplete MGMT. In patients with MGMT promoter methylation GB, this treatment proved to have an elevated survival outcome. Overall, there was longer survival for the temozolomide-lomustine combination over SOC in a randomized phase III clinical trial (CeTeG). This finding shows that different alkylating agents may have actual synergistic properties that merit further investigation [38][41].

For now, TMZ remains the first-line treatment for primary and recurrent GB management, particularly for MGMT promoter-methylated tumors. Recurrences can be treated with other alkylating drugs, such as nitrosoureas like lomustine. In any case, combined chemotherapy regimens, or increased TMZ doses, have limited advantages and higher toxicity.

4.4. Tumor-Treating Fields (TTFs)

Tumor-treating fields are a newly approved physical treatment that uses transducer arrays applied directly to the scalp to give low-intensity (1–3 V/cm), intermediate-frequency (200 kHz) alternating electric fields to treat newly diagnosed or recurring GB. TTFs generate selective toxicity in quickly dividing cells by causing neuronal depolarization and disrupting microtubule formation during mitosis. Since 2015, the FDA has approved this treatment technique as an adjunct therapy for recurrent gliomas [2][42].

A phase III trial conducted by Stupp et al. reported a PFS improvement of 6.7 months for the maintenance TMZ + TTF group versus 4.0 months for the maintenance TMZ-alone group (HR, 0.63; 95 percent CI, 0.53–0.76 [$p < 0.001$]) and an OS benefit of 20.9 months vs 16.0 months for the maintenance TMZ-alone group (HR, 0.63; 95 percent CI, 0.53–0.76 [$p < 0.001$] (HR, 0.65; 95% CI, 0.53–0.76 [$p < 0.001$]) [2][42].

TTFs have been tested in phase II and III trials in both first-time treated and recurring GB patients. PFS, OS outcomes, and objective responses improved as a result of the study. However, disagreements over study design, execution, and data interpretation have raised questions about the current evidence. Furthermore, the cost of completing the therapy is a further impediment to TTFs being used regularly [2][4][33].

There is plenty of evidence generated in the last years about the benefits of TTFs in GB. This therapy currently represents a potential alternative for the management of newly diagnosed and recurrent GB patients. However, despite the advances, the debate remains open about the limitations of this novel technique, the costs of which, together with its poor accessibility, have limited its regular application in most neuro-oncologic centers.

4.5. Bevacizumab

GBs are highly vascularized tumors characterized by overexpression of vascular endothelial growth factor (VEGF), a key regulator of tumor-associated angiogenesis. VEGF is a major target recently explored in most therapeutic trials. Bevacizumab (BEV) is a humanized monoclonal antibody against VEGF that has proven a prolonged PFS (3–4 months) but not OS benefit at several phase II and III clinical trials in newly diagnosed and recurrent GB [20][33][43].

Particularly in the recurrence setting, BEV presented response rates of approximately 30% in uncontrolled phase II trials [43]. About co-adjuvant chemotherapy with BEV, a randomized phase III trial tested the combination of BEV + lomustine versus lomustine alone, and results showed an improvement in PFS without OS changes in the combination group [44][45][46].

Another common combination for recurrences is BEV + re-irradiation. Two phase III trials found that BEV + RT-TMZ combination therapy increased PFS but not OS, as in practically every clinical trial. On the other hand, re-irradiation plus BEV was studied by Kulinich et al. The results showed a significant OS improvement but no significant PFS benefit [46]. Remarkably, patients who had previously been irradiated and were given BEV presented a reduced incidence of radio-necrosis. These findings show that the efficacy of RT with BEV is highly variable. As a result, the usefulness of this combination is still up for debate, and more randomized studies will be needed to determine the benefit [16][19][20][21]. However, neither combination therapy had demonstrated OS benefit, and the mentioned regimens are only recommended after failure of bevacizumab alone [2][32].

Based on high radiological response rates and the optimistic PFS outcomes described, bevacizumab achieved FDA approval for recurrent GB in many parts of the world, such as the USA, Canada, and Switzerland, but its effects on tumor biology and growth dynamics remain controversial [20][32]. Its failure, in clinical trials, to demonstrate an OS benefit has either stopped approval of BEV therapy for newly diagnosed GB management or has slowed down the approval process, as has happened in many regions, such as the European Union, where it remains not approved, even in the recurrence setting [33].

A relevant aspect of BEV is how it affects patients' cognitive abilities, symptoms, and quality of life. There is strong evidence that patients using BEV had worse scores on objective tests of neurocognitive function and reported cognitive function compared to placebo, implying either undiscovered tumor progression or BEV-related neurotoxicity. Furthermore, among patients who did not have tumor development on imaging investigations, those initially treated with BEV reported a worsening in the severity of their symptoms, as measured by both patient-reported outcomes and symptom-related interference with daily activities [47]. On the other hand, some research suggests that BEV patients have a considerably longer deterioration-free life than placebo patients after a year of treatment. When examining cognitive functioning, emotional functioning, role functioning, weariness, visual dysfunction, weakness in both legs, hair loss, bladder control, and financial difficulties, patients in the BEV group have a considerably longer time before deterioration [43]. Thus, more data is necessary to determine the real impact of BEV on patients' symptoms and quality of life.

As far as evidence suggests, BEV has recently been included among the main systemic treatment options for GB progression or recurrence after its approval by the FDA as a viable therapeutic alternative. This anti-angiogenic therapy has been subjected to different trials combined with novel immunological therapies presented further in the text.

4.6. Standard of Care

The current guidelines for newly diagnosed IDH-wildtype GB, WHO grade 4, treatment agree to indicate maximal safe resection as the first step in all patients. For younger patients aged <70 years with a good performance status (KPS > 70) the surgery must be followed by involved-field RT (60 Gy in 1.8–2.0 Gy fractions) + TMZ (75 mg/m2 daily throughout RT, including weekends) + 6 cycles of maintenance temozolomide (150–200 mg/m^2, 5 out of 28 days) + TTFs. An alternative in MGMT promoter-unmethylated tumors is surgical resection and RT alone. For poor performance status (KPS < 70) hypo-fractionated RT (40 Gy in 15 fractions) + TMZ or TMZ alone or best supportive care (BSC) are considered. Limiting the addition of TMZ for patients with MGMT promoter-methylated GB is to be considered [1][48].

For aged patients (>70 years) with good performance status, a regimen of RT + concomitant TMZ followed by TMZ maintenance + TTFs is recommended after GTR. The use of TMZ alone in MGMT promoter-methylated tumors is an acceptable alternative. TMZ alone or BSC is suggested for patients with low-performance status [2][33]. Accelerated hyper-fractionated, hypo-fractionated, brachytherapy, radiosurgery, or stereotactic radiotherapy are not, at this time, considered superior to average radiation in OS [33][48].

The SOC for recurrences or relapses is not well established. It is usually chosen based on the first therapy used and prognostic markers, such as age, KPS, MGMT promoter methylation status, and disease development trends. A second surgery, systemic therapy, BSC, re-irradiation, or TTFs are all indicated as alternatives in this case. BEV, TMZ rechallenge, nitrosoureas, such as lomustine/carmustine, and a combination of BEV and chemotherapy are the main systemic alternatives, but their impact on OS is still unclear [23][33][34][48].

On the other hand, BEV has not been approved to treat newly diagnosed GB but could be helpful in large and highly symptomatic tumors that might not otherwise tolerate RT [4]. The immunotherapy approach continues to be studied in several clinical trials, which are mentioned below.

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