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# The Systemic Treatment of Glioma

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## Abstract

Gliomas have been treated by a specialized team including neurosurgery, radiation therapy, and neuro-oncology, as well as depending on integrated sophisticated facilities and multi-professional team. Despite these huge efforts to glioma treatment, glioblastoma, one of the most frequent gliomas, has median life expectancy for just 15 months, so these results are still an unmet need. Related to the systemic treatment, some cancer approaches have been revolutionized with new strategies, such as immunotherapy, although in neuro-oncology, this alternative still has challenges to overcome. Throughout this chapter, relevant information and key points will be discussed to the best way to manage systemic treatment and improve glioma overall survival.

**Keywords:** gliomas, glioblastoma, astrocytoma, oligodendroglioma, immunotherapy, systemic treatment, chemotherapy

## 1. Introduction

Gliomas are the most common primary brain tumors [1]; their origin is from glial cells, i.e., from astrocytes, oligodendrocytes, and ependymal cells. Usually, it has diffused appearance, and depending on their molecular features, they may have different behaviors. The worst evolution is related to glioblastoma, in which the best treatment might provide the dismal evolution in 15 months of overall survival (OS) [2]. On the other hand, even with diffuse infiltration, when there are astrocytic features, the OS might be up to 7 years, and with oligodendroglial features [3, 4], the OS is around more than 10 years. So, these diseases are very heterogeneous in regard to pathogenesis, histopathology, and molecular and clinical features.

Related to glioma treatment, for the optimization of results [5], it is necessary to be aware of clinical variables, such as age, sex, Karnofsky Performance Status on admission, isocitrate dehydrogenase 1/2 mutation ratio, or resection rate. Besides, there is a necessity of engaged and specialized staff of neurosurgeons, radiation therapist, neuro-oncologist, anesthetist, radiologist, and a supportive staff, in an equipped and organized structure with facilities for brain tumor care.

The systemic approaches make part of glioma treatment, using drugs with direct action in tumor cells [6, 7], in association with radiation therapy [2] aiming to potentialize it, as an adjuvant therapy [8], and currently for action in the vascular formation [9, 10] and to modulate immune system.

## 2. Challenges for drug efficacy in CNS tumors

The preferred treatment for brain tumors has been attempting to maximize the degree of surgical resection. But irrespective of the relevance of this approach, it

has limitations with respect to gliomas due to the invasiveness of these tumors and their tendency to reside in or near important brain areas. Traditional postsurgical therapy for gliomas involved standard radiation therapy and chemotherapy. There are some issues which might be considered as a challenge to improve glioma treatment.

### **2.1 Blood-brain barrier (BBB), blood-cerebrospinal fluid barrier (blood-CSFB), and blood-tumor barrier**

Anatomically, CNS can be subdivided into the parenchyma, meninges, special sense organs, cranial nerves, spinal nerves, and the ventricular system with its contents. All these structures are limited by boundaries under normal conditions, such as blood-brain barrier, blood-CSFB, and, in pathologic scenario, blood-tumor barrier. Under normal physiology, the BBB's unique anatomic structure and the tightly regulated interplay of its cellular and acellular components allow for maintenance of brain homeostasis, regulation of influx and efflux, and protection from harm; these characteristics ensure an optimal environment for the neural network to function properly. It is not really a barrier but rather a communication "center," responding to and passing signals between the CNS and blood [11]. It is constituted by cells that surround the vessels, the endothelium cells, which have been considered the central unit, and there is a growing understanding in the interactions of this central cell with other cells and systems, such as pericytes [12], astrocytes [13], and microglia. The integration among them results in maintenance of BBB permeability. There is a vast research to study the relation between this complex system and pathologies. Under pathologic conditions, these barriers might lose their permeability allowing easy traffic between the compartments.

Charge, lipophilicity, and molecular size are key issues for drugs to pass through BBB. Drugs currently in use for CNS tumors, for example, temozolomide and lomustine, can reach, despite BBB permeability, in areas with neoplastic enhancement in imaging studies, which might have dysfunctional BBB and permit some drugs to get in easily.

For instance, BBB is part of complex environment that supports the balance and homeostasis of CNS, and it is as well a barrier both to drugs and chemotherapeutic agents and to immunotherapeutic agents.

### **2.2 Drug development**

The best quality preclinical testing model would select appropriate molecular targets, determine the effectiveness of drugs directed against those targets and the ideal genetic and cellular context for their use, evaluate the toxicity of selected drugs, and identify relevant biomarkers demonstrating drug efficacy and specificity to assist in subsequent clinical trials [14].

At the laboratory level, there are limitations of drug development for gliomas. Preclinical tests might be performed in *in vitro* tests or in animal model tests. In *in vitro* tests, there are limitations owing to cellular homogeneity that could not reproduce the real tumor environment and cellular heterogeneity; moreover, the systemic influences affect drug metabolism and distribution, and what's more, in an animal model in which are based on xenografts inserts in flank or directly into the animal brain. But these models, despite working in preclinical models, usually fail to reproduce the same result at the clinical level. Another strategy that has been developed by using genetically engineered mouse models (GEMMs) [15] has shown that glial tumors spontaneously develop, mostly of high grade, after a variable

latent period. Such GEMMs are the best current models we have for approximating the biology of CNS neoplasms in humans.

Other efforts have been made in order to better understand the overlap of various models and human brain tumor behavior; in recent published paper [16], the authors have studied the differences and similarities in glioma biology as conveyed by transcriptomic patterns across four mammalian hosts: rats, mice, dogs, and humans. And they have found notable differences that were observed in gene expression patterns as well as related biological pathways and cell populations known to mediate key elements of glioma biology, including angiogenesis, immune evasion, and brain invasion.

### **2.3 Tumor heterogeneity**

Tumor heterogeneity may keep tumor evolution and adaptation, which prevent personalized medicine agents to work [17]. It has been described in various tumor models, and this feature in gliomas allowed them to be resistant to several known drugs [18, 19].

There is a growing knowledge in the molecular and cellular basis of glioblastoma; Diane J. Aum [18], in her paper, introduced emerging concepts on the molecular and cellular heterogeneity of glioblastoma and laid emphasis that we should begin to consider each individual glioblastoma to be an ensemble of distinct subclones that reflect a spectrum of dynamic cell states. And this knowledge partially explains this entity's resistance to treatment, as well as allows new researches and strategies to overcome it.

### **2.4 Immunosuppressive environment of brain tissue**

A detailed understanding of the supportive role that the microenvironment plays in glioblastoma (GBM) is critical to the design of effective immunotherapeutic strategies. Glioma histology shows that >30% of GBM tumors are composed of infiltrating microglia [20] with active recruitment of peripheral macrophages [21]. The secretion of immunomodulatory cytokines from GBM cells, including interleukins 10 (IL-10), 4 (IL-4), and 6 (IL-6), and, particularly, tumor growth factor-beta (TGF- $\beta$ ) in addition to prostaglandin E2 can suppress microglia activation.

Tumor-associated macrophages (TAM) [22] are often considered to be facilitators of tumor growth because of their proangiogenic and immunosuppressive properties. Besides it, the glioma tumor cells are between the least immunogenic in the spectrum of the human tumors, which confer then to be less responsive to immunotherapy [23].

Therefore, a complex system allows tumor cells to grow without immune system control, and this knowledge opens new avenues to exploration of immunotherapeutic issues.

## **3. Glioma classification**

The new version of the World Health Organization Classification of Tumors of the Central Nervous System (WHO 2016) [24] introduced the concept of an integrated diagnosis, based on a union of both phenotypic (microscopic) and genotypic parameters. Major changes are seen in glioma and medulloblastoma groups. Fewer entities are included and some, related to their no longer diagnostic and therapeutic relevance, were deleted.

In the previous version, WHO 2007, all astrocytic tumors had been grouped together, but now in new 2016 classification, all diffuse gliomas whether they are astrocytic or oligodendroglial are grouped under one heading, mainly based on their growth pattern, behavior, as well as a mutation in IDH.

Regarding the histological classification at the WHO 2016, there were few modifications; tumors are still being classified as grade I, II, III, and IV; and just a new category “grade unknown” is added for diffuse leptomeningeal glioneuronal tumor [25].

### 3.1 Nomenclature

The nomenclature of the combination of histopathological and molecular features must be standardized to simplify its use; CNS tumor diagnoses should consist of a histopathological name followed by the genetic features, with the genetic features following a comma and as adjectives, as in *diffuse astrocytoma*, IDH *mutant*, and *medulloblastoma*, wingless (WNT) *activated*. If there are more than one genetic features, it must be included in the description, for example, *oligodendroglioma*, IDH *mutant* and *1p/19q co-deleted*. When the tumor has no genetic alteration, the term “wild type” might be used if an official entity already exists, for example, *glioblastoma* IDH *wild type*.

For situations which there are no access to molecular tests, or it was not done, by whatever reason, the term not otherwise specified (NOS) must be used, for example, *diffuse astrocytoma*, NOS. For instance, the NOS terminology refers to an incomplete or unavailable information related to molecular tests.

### 3.2 Gliomas

Despite having astrocytic or oligodendroglial features, in the WHO 2016, they are grouped together as diffuse gliomas, and for pathologic point of view, it is useful, so they are grouped together; for prognostic issues and patient management, the therapeutic orientation might be driven biologically and genetically.

Astrocytic gliomas include diffuse lesions, which may be grade II, grade III (anaplastic), and grade IV (glioblastoma), and main molecular features are IDH and alpha-thalassemia/mental retardation syndrome X-linked (ATRX) gene. IDH-mutated lesions may have better evolution. Grades II and III are mainly IDH mutated, whereas grade IV (glioblastoma) is predominately IDH wild type.

Oligodendroglial tumors have their histological features; although astrocytic ones might have its feature as well, and its molecular features are IDH mutated and 1p/19q co-deleted, these classes of tumors have better prognosis. It may have grade II and grade III (anaplastic). When the genetic tests are not available, it will be classified as diffuse astrocytoma, NOS; oligodendroglioma, NOS; or glioblastoma, NOS.

## 4. Glioma molecular markers

### 4.1 IDH1 and IDH2

IDH is the most important diagnostic marker as it can differentiate glioma from gliosis. These mutations have affected amino acid 132 of isocitrate dehydrogenase 1 gene (IDH1) in more than 70% of the WHO grade II and III astrocytomas and oligodendrogliomas and in glioblastomas that have developed from these lower-grade lesions [26].



Two IDH variants have been used, IDH1 and IDH2, which are enzymes in Krebs cycle that catalyzes the conversion of isocitrate to alpha-ketoglutarate. IDH1 mutations are heterozygous, and these are involving an amino acid substitution (glycine to arginine) in the active site of the enzyme in codon 132 (R132H). This mutation results in the abnormal production of 2-hydroxyglutarate, which causes histone and deoxyribonucleic acid (DNA) methylation, hence promoting tumorigenesis [27], while IDH2 variants are reported to influence angiogenesis, apoptosis, and glucose metabolism [28].

IDH can be demonstrated by IDH1 or IDH2 mutation by immunohistochemistry using mutation-specific antibody against R132H-mutant IDH1; if immunostaining is negative, then it should be followed by IDH1/IDH2 DNA genotyping. Mutation in both IDH1 and IDH2 entities is known as IDH mutant. When both are negative, then it is known as IDH wild type. If IDH testing is not available or cannot be fully performed or is inconclusive, then it is labeled as IDH NOS.

#### **4.2 1p/19q co-deletion**

In 1p/19q co-deletion, there is a complete deletion of both the short arm of chromosome 1 (1p) and the long arm of chromosome 19 (19q). 1p/19q co-deletion can be demonstrated by fluorescent *in situ* hybridization (FISH), polymerase chain reaction, chromogenic *in situ* hybridization, or molecular genetic testing. It is definitive for the diagnosis of grade II and grade III (anaplastic) oligodendrogliomas. It is a strong prognostic factor associated with improved survival and also a predictive factor for response to chemotherapy as well as radiotherapy [29, 30].

#### **4.3 O6-methylguanine-DNA methyltransferase methylation (MGMT)**

The MGMT gene encodes a DNA repair enzyme that can nullify the effects of alkylating chemotherapy such as temozolomide [31]. The alkylating chemotherapy damages DNA by adding methyl groups. Therefore, a tumor with a high degree of MGMT activity will be resistant to chemotherapies which target DNA at this location. If the promoter region of the MGMT gene is unmethylated, the gene will be active, whereas if the promoter region of MGMT is hypermethylated, the gene will be silenced. However, if the MGMT gene is active, the damage is rapidly repaired. Methylation of the MGMT gene promoter is a favorable prognostic and predictive factor in glioblastoma patients, but it is not a diagnostic marker for the same.

The correlation with other biomarkers is mandatory to have oriented treatment in neuro-oncology [32].

#### **4.4 TERT (telomerase reverse transcriptase) promoter mutations**

TERT mutations often involve C228T and C250T mutations of the promoter region. TERT promoter mutations and long telomere length predict poor survival and radiotherapy resistance in gliomas. It occurs mainly in glioblastoma and oligodendroglioma. TERTp and IDH mutations are routinely used clinically to facilitate diagnosis by classifying 80% of GBMs into molecular subgroups with distinct clinical courses [30, 33].

#### **4.5 Alpha-thalassemia/mental retardation syndrome X-linked (ATRX)**

It is a chromatin-remodeling protein important in DNA replication, telomere stability, gene transcription, chromosome congression, and cohesion during cell

division. ATRX mutation results in lengthening of telomerase which helps in chromatin maintenance and remodeling. All cells are ATRX positive. If ATRX mutation is present, then there will be a loss of staining in the cells [34].

ATRX mutations are almost always accompanied by other mutations in the histone regulation (IDH, H33 K27M, tumor protein p53 [TP53], etc.) [35]. Loss of ATRX expression is seen in 45% of anaplastic astrocytoma, 27% of anaplastic oligoastrocytoma, and 10% of anaplastic oligodendroglioma and also in pediatric and adult high-grade astrocytoma [36].

#### 4.6 Tumor protein p53

p53 is a tumor suppressor gene located on the short arm of chromosome 17. Loss of p53 leads to DNA damage, hypoxia, oncogene activation, microtubule disruption, and oxidative damage which in turn contributes to the CNS tumor pathogenesis mainly medulloblastoma, glioblastoma, and in 56–58% of IDH-mutant astrocytoma [37]. Copy number neutral loss of heterozygosity of chromosome 17p (CNLOH 17p) was nearly exclusively associated with IDH1-mutant astrocytoma with TP53 mutations. “CNLOH” means that one copy of the chromosome has been deleted, whereas the remaining copy has been duplicated. The net result is that the cell still has a total of two copies of the gene or chromosomal segment, but instead of having two different copies, a single copy has been duplicated. CNLOH 17p was found to be a significant prognostic factor, with better survival outcomes for those with the CNLOH 17p alteration [38].

### 5. Low-grade gliomas

Usually, the term “low-grade glioma” refers to the glioma class, which has an indolent evolution and an incurable disease, and during their evolution transform into a high grade. It has a specific molecular and genetic profile. In the WHO 2016, they are represented by diffuse astrocytic glioma grade II, IDH mutant and IDH wild type, and diffuse oligodendroglioma, IDH mutant with 1p/19q co-deletion or not [39].

Surgery is a key point on its management, getting tissue for biopsy and molecular analysis, and the timing depends on some variables, such as tumor size, localization, age of patient, and symptoms. Patients with small tumors might be followed regularly; despite not having randomized studies, early intervention has been showing OS advantages, as well the extension of resection and maximum safe resection rather than partial resection or biopsy [40–42].

Radiation therapy is an important part of the low-grade glioma treatment, and the optimal timing is controversial; by the way, for those ones with high risk of relapse, the immediate delivery of radiation is of the standard approaches [43].

Regarding the systemic treatment, chemotherapy is part of its treatment in the adjuvant and at relapse setting of the low-grade glioma spectrum.

In RTOG 9802, patients were randomly assigned to radiation therapy (RT) alone or RT followed by six cycles of procarbazine, lomustine, and vincristine (PCV). The primary endpoint was OS, and the secondary endpoint was PFS and grade III toxicity. At the time of the first publication [44] with a median follow-up of 5.9 years in surviving patients, there was a trend toward longer survival in the RT plus chemotherapy group (5-year overall survival 72 vs. 63%, hazard ratio [HR] 0.72, 95% CI 0.47–1.10), but with a median follow-up of 11.9 years showed at second publication [45], the significance of OS and progression-free survival (PFS) was reached, with median overall survival 13.3 vs. 7.8 years for patients treated with RT followed by

PCV, HR 0.59,  $p = 0.03$ , and the median progression-free survival was also prolonged in patients who received PCV (10.4 vs. 4.0 years,  $p = 0.002$ ).

These results bring level 1 evidence to treat high-risk patients with low-grade gliomas with RT and PCV. As PCV is toxic and there are further evidences of equivalences with temozolomide [46], despite not being randomized by studies comparing it in this population, this drug can be used with the 2B level of evidence. At CATNON trial, there was a comparison in patients with anaplastic oligodendrogliomas with no co-deletion, between RT and RT followed by temozolomide, with OS advantage.

In the subgroup of patients who had had 1p/19q co-deletion, the significance of benefit from PCV was greater in patients with oligodendroglioma ( $n = 101$ ; HR 0.43, 95% CI 0.23–0.82) and oligoastrocytoma ( $n = 77$ ; HR 0.56, 95% CI 0.32–1.0) than in those with astrocytoma ( $n = 46$ ; HR 0.73, 95% CI 0.40–1.34).

## 6. High-grade gliomas

This category is composed by grade III diffuse gliomas (anaplastic astrocytoma, anaplastic oligodendroglioma) and grade IV (glioblastoma). Typically, the symptom evolution occurs in few weeks or months. Among them, there are different prognoses, so as anaplastic oligodendroglioma has OS of 9 years, anaplastic astrocytoma has OS of 3–5 years, and glioblastoma has OS of just 15 months. The prognosis will be dependent on age, performance status, localization of the lesion, grade of resection [47, 48], and molecular profile for grade III diffuse gliomas (IDH and 1p/19q co-deletion) and for glioblastoma (IDH status, MGMT, TERT, p53, epidermal growth factor receptor variant III (EGFRvIII), and others).

Surgery for high-grade gliomas has the goal of maximum safe resection [49], with prognosis improvement, or at least partial resection or stereotactic biopsy to define histology, as well as molecular markers to drive treatment. Many strategies have been tested to reach maximum safe resection, such as awake surgery, intra-operative magnetic resonance [50], 5-aminolevulinic acid (5-ALA) guide surgery [48], and other techniques that require expertise and facilities to deal with these demands.

Further adjuvant treatment, considering gold standard, using radiation therapy and systemic treatment is required. To revisit this issue, it might be considered that previous trials took data from a mix of histologic and molecular subtypes, not taking in account the updated WHO 2016.

### 6.1 Grade III diffuse gliomas

#### 6.1.1 Anaplastic oligodendroglioma

In this subtype, the knowledge of the role of 1p/19q co-deletion as better prognostic marker as far has been demonstrated [51]. According to the WHO 2016, this tumor must have IDH mutation and 1p/19q co-deletion.

One of the evidences to treat this class of patient with combination of radiation therapy and chemotherapy was demonstrated in EORTC brain tumor group study 26951 [29], where 368 adult patients with newly diagnosed anaplastic oligodendroglial tumors were randomly assigned to either RT or the same RT followed by six cycles of adjuvant PCV, and with a median follow-up of 140 months, OS in the RT/PCV arm was significantly longer (42.3 vs. 30.6 months in the RT arm, hazard ratio [HR], 0.75; 95% CI, 0.60–0.95). In an exploratory analysis of 80 patients with a 1p/19q co-deletion, OS was increased, with a trend toward more benefits



from adjuvant PCV (OS not reached in the RT/PCV group vs. 112 months in the RT group; HR, 0.56; 95% CI, 0.31–1.03). IDH mutational status was also of prognostic significance.

At RTOG 9402 in an updated publication [52], 291 patients with anaplastic oligodendrogliomas and pure (AO) and mixed (anaplastic oligoastrocytoma (AOA)) were randomized to four cycles of PCV followed by radiation therapy (RT). For the entire cohort, there was no difference in median survival by treatment (4.6 years for PCV plus RT vs. 4.7 years for RT), but for 1p/19q co-deleted patients as in EORTC 26951, there was survival benefit, although this analysis was not preplanned.

### 6.1.2 Anaplastic astrocytoma

In the WHO 2016, anaplastic astrocytoma molecular feature is IDH1/IDH2 mutated and IDH1/IDH2 wild type, with no 1p/19q co-deletion. Anaplastic astrocytoma IDH1/IDH2 wild type has worse prognosis than the IDH1/IDH2 mutated [25].

At CATNON trial (EORTC study 26053-22054) [8], 745 patients (99%) of the planned 748 patients, with anaplastic astrocytoma with no 1p/19q co-deletion, had been enrolled in a four-arm study comparing RT alone, RT with concurrent daily temozolomide, RT followed by 12 cycles of adjuvant temozolomide, and RT with both concurrent and 12 cycles of adjuvant temozolomide. At the interim analysis of RT × RT followed by 12 cycles of adjuvant temozolomide, the temozolomide addition had a significant improvement in both progression-free survival (HR 0.62, 95% CI 0.50–0.76) and overall survival (median 44.1 months vs. not yet reached; HR 0.65, 95% CI 0.45–0.93).

So, based upon CATNON trial and other observations [53, 54], patients with anaplastic astrocytoma must be treated with adjuvant RT and chemotherapy, and if IDH is wild type, it must be treated as glioblastoma. To IDH-mutated lesions, until final analysis of CATNON trial, there is no evidence-based data supporting concomitant adjuvant treatment for this subgroup.

## 6.2 Grade IV gliomas: glioblastoma

Glioblastoma has been a daily challenge for those who attend these patients, as well for those who are involved in research area. Glioblastoma is the most common glioma and usually has dismal evolution in few months or years, so it has OS of just 15 months. At the Stupp trial [2], in the current standard of care of postoperative therapy for glioblastoma, 573 newly diagnosed patients with histologically confirmed glioblastoma were randomly assigned to receive radiotherapy alone or radiotherapy plus continuous daily temozolomide, followed by six cycles of adjuvant temozolomide. At a median follow-up of 28 months, the median survival was 14.6 months with radiotherapy plus temozolomide and 12.1 months with radiotherapy alone. The unadjusted hazard ratio for death in the radiotherapy plus temozolomide group was 0.63 (95% confidence interval, 0.52–0.75;  $P < 0.001$  by the log-rank test).

At this trial and others [55, 56], MGMT-methylated patients are doing better, and this biomarker became a strong predictor of temozolomide response.

Low-intensity alternating electric field therapy (TTFields) is a novel treatment to glioblastoma, in which locoregionally delivered antimitotic treatment interferes with cell division and organelle assembly. This stimulus is delivered continuously by transducers applied to a shaved scalp. In an open-label randomized trial of 695 adults with newly diagnosed glioblastoma, median survival was improved in patients assigned to wear the device during the adjuvant temozolomide phase of

standard chemoradiation compared with those assigned to standard chemoradiation alone (21 vs. 16 months) [57, 58]. The requirement to carry a device and maintain a shaved scalp for the duration of treatment presents a potential burden that is not acceptable to all patients [59].

On a phase II study [60], 39 glioblastoma patients are offered with radiotherapy of tumor site only and CCNU/TMZ (carmustine/temozolomide) chemotherapy for up to six courses. It results in a longer survival when compared to historical controls, mainly in MGMT-methylated patients; in the whole cohort, the median overall survival (mOS) was 23.1 months, and comparing MGMT methylated or not, the mOS was significantly longer with 34.3 vs. 12.5 months. The WHO grade IV hematologic toxicity was frequent.

CeTeG/NOA-09 trial was designed to prove that MGMT-methylated glioblastoma patients might have better survival using CCNU/TMZ. In this trial, there was randomization between MGMT-methylated glioblastoma patients to treat with a standard Stupp protocol vs. six cycles of CCNU/TMZ, its results were presented at plenary section of 22nd SNO (Society of Neuro-oncology meeting) [61], and it results in mOS for TMZ of 30.4 and 46.9 months for CCNU/TMZ. These are challenging results, waiting for publication for further details.

## 7. New strategies to treat gliomas

In the last 30 years, there have been huge investments in glioma research for better outcomes; despite being fruitful, it is far from being solved. There are studies in anti-angiogenic drugs, inhibition of integrins, inhibition of growth factor receptors and intracellular signaling pathways, and immunotherapy, and despite failing to improve OS, immunotherapy has demonstrated hopeful results.

Immunotherapy has been extensively studied, with better understanding of relationship between tumors and immune system [62], and it is totally clear that immune system plays a key role in the tumor evolution as well as its control. Currently, immunotherapy has been standard in a growing spectrum of tumors [63, 64].

Immunotherapy challenges in glioblastoma, owing to low mutational load (TML) and therefore potential immunogenicity, and tight immune regulation within the CNS result in limited T-cell effector responses, which means that immunosuppressive microenvironment and blockade of some cells to CNS have been limited for better use of this strategy in glioma field.

### 7.1 Vaccines

As an active immunotherapy (vaccine), rindopepimut (Rintega) consists of an EGFRvIII peptide conjugated to keyhole limpet hemocyanin, which is expressed in 30% of cells from glioblastoma patients and was previously tested in a phase II trial (ACT III) [65], and it had been the first immunotherapeutic to demonstrate increased survival. The hypothesis had been tested in a phase III trial, ACT IV [66], in which patients with newly diagnosed GBM with EGFRvIII expressed treated with standard chemoradiation with or without rindopepimut. Its publication showed that there was no difference at primary endpoint, with OS of 20.4 vs. 21.1 months. There are some evidences of association between bevacizumab and rindopepimut having synergistic effect [67], but this hypothesis must be proven.

Another provocative strategy has just been published [68] in a phase III trial which evaluates the addition of an autologous tumor lysate-pulsed dendritic cell vaccine (DCVax®-L) to standard therapy for newly diagnosed glioblastoma.

The final results are not yet available, because they are still unblinded, until the sufficient events have occurred to elucidate the final curves. Despite being an interim analysis, it has been shown 23.4 months of medium OS (mOS), as the intention-to-treat (ITT) population is similar, and it was allowed to crossover. So, we have to wait for the final data.

## 7.2 Checkpoint inhibitors

Another promising area is immunotherapy with checkpoint inhibitors, although a recent trial failed to demonstrate survival benefit. The CheckMate 143 was the first randomized phase III clinical trial in GBM with a PD-1 checkpoint inhibitor. In nivolumab alone vs. bevacizumab alone in recurrent GBM, 369 patients were randomized to the nivolumab (n = 184) or bevacizumab (n = 185), resulting in a median OS of 9.8 months with nivolumab and 10 months with bevacizumab, and the 12-month OS rate was 42% in both arms. Despite having failed to demonstrate advantage, in a specific scenario, in patients with biallelic mismatch repair deficiency (bMMRD), it can benefit from checkpoint inhibitor treatment [69]. This might be explained by a high mutational burden in bMMRD. In other considerations, CheckMate 143 failure involves an inability of nivolumab to reach tumor-infiltrating lymphocytes (TILs) already sequestered in the recurrent tumor microenvironment; it may be expected to function better in patients with newly diagnosed GBM, where newly activated circulating T cells would be available for interaction with nivolumab prior to their migration to tumor sites. So, further investigation is required to set PD-1 checkpoint in glioma treatment [70, 71].

## 7.3 CAR T cells

Tumor immunotherapy with T lymphocytes, which can recognize and destroy malignant cells, has been limited by the ability to isolate and expand T cells restricted to tumor-associated antigens. Chimeric antigen receptors (CARs) composed of antibody-binding domains connected to domains that activate T cells could overcome tolerance by allowing T cells to respond to cell surface antigens; however, to date, lymphocytes engineered to express CARs have demonstrated minimal in vivo expansion and antitumor effects in clinical trials [72]. The very begging publications related to CAR T-cell therapy were related to a relapsed and refractory acute lymphoblastic leukemia, which made this technology known.

At glioma setting, CAR T-cell therapy has been tested, in recurrent GBM utilizing CAR T-cell GBM-associated antigen IL13Ra2 that utilizes CD62L-enriched central memory T cells (T<sub>cm</sub>) engineered by lentiviral transduction to express [73]. Second-generation 4-1BB-containing CAR (IL13BBZ) signaling domain was utilized by both intratumoral and intraventricular deliveries, with multiple doses via reservoir. Safely and well tolerated, some dramatic responses were observed, both in brain and meninx lesions.

Further efforts have been made to improve results of this therapy [74–76].

## 7.4 Cancer-targeting oncolytic viruses

Cancer virotherapy mediated by oncolytic viruses (OV) has emerged as a novel and effective strategy in cancer therapeutics [77]. Desjardins [78] in a dose-finding and toxicity phase I study evaluated an intratumoral delivery of the recombinant nonpathogenic poliovirus-rhinovirus chimera (PVSRIPO). PVSRIPO recognizes the poliovirus receptor CD155, which is widely expressed in neoplastic cells of solid tumors and in major components of the tumor microenvironment. Overall survival

among the patients who received PVSRIPO reached a plateau of 21% (95% confidence interval, 11–33) at 24 months that was sustained at 36 months. For glioma grade IV with standard treatment, there is no plateau. A phase II study in this setting is ongoing NCT02986178.

## 8. Conclusions

Glioma treatment is still a challenge, and its quality is related to integrated team, in which the systemic treatment must be based on awareness of drug limitation usage and keeping in mind strategies to overcome these issues.

## Conflict of interest

The author declares no conflict of interests.

## Notes/thanks/other declarations

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