

Potential roads for reaching the summit: an overview on target therapies for high-grade gliomas

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Abstract. *Background:* The tailored targeting of specific oncogenes represents a new frontier in the treatment of high-grade glioma in the pursuit of innovative and personalized approaches. The present study consists in a wide-ranging overview of the target therapies and related translational challenges in neuro-oncology. *Methods:* A review of the literature on PubMed/MEDLINE on recent advances concerning the target therapies for treatment of central nervous system malignancies was carried out. In the Medical Subject Headings, the terms “Target Therapy”, “Target drug” and “Tailored Therapy” were combined with the terms “High-grade gliomas”, “Malignant brain tumor” and “Glioblastoma”. Articles published in the last five years were further sorted, based on the best match and relevance. The ClinicalTrials.gov website was used as a source of the main trials, where the search terms were “Central Nervous System Tumor”, “Malignant Brain Tumor”, “Brain Cancer”, “Brain Neoplasms” and “High-grade gliomas”. *Results:* A total of 137 relevant articles and 79 trials were selected. Target therapies entailed inhibitors of tyrosine kinases, PI3K/AKT/mTOR pathway, farnesyl transferase enzymes, p53 and pRB proteins, isocitrate dehydrogenases, histone deacetylases, integrins and proteasome complexes. The clinical trials mostly involved combined approaches. They were phase I, II, I/II and III in 33%, 42%, 16%, and 9% of the cases, respectively. *Conclusion:* Tyrosine kinase and angiogenesis inhibitors, in combination with standard of care, have shown most evidence of the effectiveness in glioblastoma. Resistance remains an issue. A deeper understanding of the molecular pathways involved in gliomagenesis is the key aspect on which the translational research is focusing, in order to optimize the target therapies of newly diagnosed and recurrent brain gliomas. (www.actabiomedica.it)

Key words: Glioblastoma; Malignant Brain Tumors; Neuro-Oncology; Target Therapy; Tyrosine Kinase Inhibitors.

Background

High-grade gliomas, with glioblastoma (GBM) being the progenitor, are the most lethal primary brain tumors of all because of the certainty of recurrence and mortality.¹⁻⁴ As a matter of fact, the median overall survival is no longer than 15 months, despite current

multimodality treatment including surgery, radiotherapy and chemotherapy.^{5,6}

The significant resistance of GBM to therapy is related to the heterogeneous genetic landscape of the tumor. High-grade gliomas harbor recurrent molecular abnormalities which are involved in the maintenance of the cell's cycle and growth, the tumor

microenvironment, pathological angiogenesis, DNA repair and apoptosis.⁷⁻¹⁰

Advances in genetics and the studies of epigenetics in many pathologies affecting the central nervous system (CNS) have allowed the molecular characterization, as well as the identification of the anomalies in the cellular signaling pathways¹¹⁻¹⁴. The same insights have been of utmost importance also in neuro-oncological field, GBM first, where they led to a better understanding of tumor progression and cancer drug escape.¹⁵⁻²⁰ A deeper understanding of the malignant GBM phenotype has recently improved the knowledge about the biology of cancer, which is the starting point for identifying specific biomarkers and for developing new agents for targeting specific steps in the transduction pathways of glioma cells.²¹ Novel tailored therapies include drugs aimed at counteracting the effects of the neoplastic genetic deregulation, pathological angiogenesis and growth factor receptors; the latter with their downstream signaling pathways.

An overview of the target therapeutic strategies and challenges in developing effective agents is reported as follows.

Methods

The search of the literature was performed on the PubMed/MEDLINE (<https://pubmed.ncbi.nlm.nih.gov>) search engine, with combinations of Medical Subject Headings (MeSH) terms and text words, and on the ClinicalTrials.gov website (<https://clinicaltrials.gov>). The MeSH terms “Target Therapy”, “Target drug” and “Tailored Therapy” were combined with the MeSH terms “High-grade gliomas”, “Malignant brain tumor” and “Glioblastoma”. In addition to original articles, our research involved reviews and editorials. The sorting of articles was carried out focusing on the most relevant studies chosen according to titles and abstracts.

On the ClinicalTrials.gov database the text words “Central Nervous System Tumor”, “Malignant Brain Tumor”, “Brain Cancer”, “High-grade gliomas” and “Brain Tumor” were used for the field “condition/disease”. Only trials regarding target therapies, without restrictions for localization, study phase and recruitment

status were selected. Filtering included articles published in the last five years, in English or translated into English. A descriptive analysis was provided.

Results

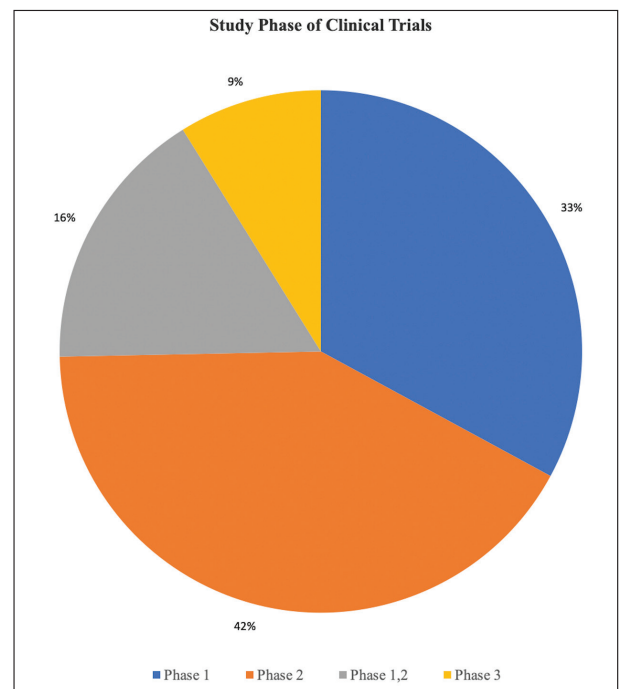
1. Volume of the Literature

The search retrieved a total of 178 articles and 148 clinical trials. After the implementation of the exclusion criteria and removal of duplicates, 137 articles and 79 randomized and non-randomized clinical trials were collected.

About the clinical trials, 33% were phase I, 42% phase II, 16% phase I/II and 9% phase III (Graph 1). Table 1 summarizes the most relevant clinical trials on target therapies for high-grade gliomas (Table 1).

2. Classification of The Target Therapies

The target therapies are mostly categorized according to the targets, which, in their turn, include molecular alterations and oncogenic signaling. The



Graph 1. Pie graph showing the distribution of the selected clinical trials according to the study phase.

Table 1. Clinical Trials on Target Therapies for High-Grade Gliomas.

#	ClinicalTrials.gov Identifier	Conditions	# of Patients Enrollment	Interventions	Study Phase	Status	Locations
1	NCT00025675	Brain and Central Nervous System Tumors	105	Gefitinib	2	Completed	USA
2	NCT00016991	Brain and Central Nervous System Tumors	53	Gefitinib	2	Completed	USA
3	NCT00238797	Glioblastoma Multiforme	36	Gefitinib	2	Completed	SW
4	NCT00027625	Brain and Central Nervous System Tumors	n/a	Gefitinib, Temozolomide	1	Completed	USA
5	NCT00418327	Malignant Brain Tumor	48	Erlotinib	1	Completed	FR
6	NCT00301418	Glioblastoma Multiforme Anaplastic Astrocytoma	11	Erlotinib	1, 2	Completed	USA
7	NCT00086879	Brain and Central Nervous System Tumors	110	Carmustine, Erlotinib, Temozolomide	2	Completed	BE, FR, IT, NL, UK
8	NCT01591577	Newly Diagnosed Glioblastoma Multiforme	50	Lapatinib, Temozolomide, Radiotherapy	2	Completed	USA
9	NCT00099060	Brain and Central Nervous System Tumors	24	Lapatinib	1, 2	Completed	CN
10	NCT02423525	Brain Cancer	24	Afatinib	1	Completed	USA
11	NCT00977431	Glioblastoma Multiforme	36	Afatinib, Temozolomide, Radiotherapy	1	Completed	UK
12	NCT01520870	Glioblastoma Multiforme Brain Tumor, Recurrent	49	Dacomitinib	2	Completed	ES
13	NCT01112527	Glioblastoma Multiforme	58	Dacomitinib	2	Completed	USA
14	NCT00463073	Malignant Gliomas	32	Cetuximab, Bevacizumab, Irinotecan	2	Completed	DK
15	NCT01800695	Glioblastoma Multiforme	202	Depatuxizumab mafodotin (ABT-414), Temozolomide, Whole Brain Radiation	1	Completed	AU
16	NCT02573324	Glioblastoma Multiforme	691	Depatuxizumab mafodotin (ABT-414), Temozolomide	3	Active, not recruiting	USA
17	NCT04083976	Advanced Solid Tumor	280	Erdaftinib	2	Recruiting	USA
18	NCT00049127	Recurrent Adult Brain Neoplasm	64	Imatinib	1, 2	Completed	USA
19	NCT00613054	Glioblastoma Multiforme	27	Imatinib, Hydroxyurea	1	Completed	USA
20	NCT01331291	Glioblastoma Multiforme	36	Bosutinib	2	Completed	USA
21	NCT00601614	Glioblastoma Multiforme Gliosarcoma	119	Temozolomide, Vandetanib	1.2	Completed	USA

#	ClinicalTrials.gov Identifier	Conditions	# of Patients Enrollment	Interventions	Study Phase	Status	Locations
22	NCT00427440	Advanced Malignant Glioma	61	AMG 102	2	Completed	USA
23	NCT01632228	Glioblastoma Multiforme	135	Onartuzumab, Bevacizumab	2	Completed	CN, FR, DE, IT, ES, SW, UK, USA
24	NCT01113398	Glioblastoma Multiforme Gliosarcoma	36	AMG 102, Bevacizumab	2	Completed	USA
25	NCT01632228	Glioblastoma Multiforme	135	Bevacizumab, Onartuzumab	2	Completed	USA
26	NCT00606879	Advanced Cancer	46	SGX523	1	Terminated	USA
27	NCT00607399	Advanced Cancer	46	SGX523	1	Terminated	USA
28	NCT00784914	Brain and Central Nervous System Tumors	12	Temsirolimus	1	Completed	USA
29	NCT00016328	Adult Glioblastoma Multiforme Adult Gliosarcoma Recurrent Adult Brain Tumor	33	Temsirolimus	2	Completed	USA
30	NCT00047073	Brain and Central Nervous System Tumors	13	Sirolimus, Surgery	1, 2	Completed	USA
31	NCT00672243	Glioblastoma Multiforme Gliosarcoma	32	Erlotinib, Sirolimus	2	Completed	USA
32	NCT00553150	Brain and Central Nervous System Tumors	122	Everolimus, Temozolomide, Radiotherapy	1.2	Completed	USA
33	NCT00085566	Brain and Central Nervous System Tumors Prostate Cancer	61	Everolimus, Gefitinib	1.2	Completed	USA
34	NCT01339052	Glioblastoma Multiforme	65	Buparlisib, Surgery	2	Completed	USA
35	NCT01473901	Glioblastoma Multiforme	38	Buparlisib, Temozolomide, Radiotherapy	1	Completed	USA
36	NCT01349660	Glioblastoma Multiforme	88	Buparlisib, Bevacizumab	1, 2	Active, not recruiting	USA
37	NCT00590954	Malignant Gliomas Brain Cancer	32	Perifosine	2	Completed	USA
38	NCT00005859	Brain and Central Nervous System Tumors	136	Tipifarnib	1.2	Completed	USA
39	NCT00049387	Adult Giant Cell Glioblastoma Adult Glioblastoma Adult Gliosarcoma	19	Tipifarnib, Temozolomide, Radiotherapy	1	Completed	USA
40	NCT00015899	Brain and Central Nervous System Tumors	53	Lonafarnib	1	Completed	USA

#	ClinicalTrials.gov Identifier	Conditions	# of Patients Enrollment	Interventions	Study Phase	Status	Locations
41	NCT00038493	Glioblastoma Multiforme	23	Temozolomide, Lomafarnib	2	Completed	USA
42	NCT01748149	Pediatric BRAFV600E-mutant Gliomas	40	Vemurafenib	1	Active, not recruiting	USA
43	NCT02345824	Glioblastoma Glioma	3	Ribociclib	1	Active, not recruiting	USA
44	NCT02896335	Metastatic Malignant Brain Tumors	30	Palbociclib	2	Recruiting	USA
45	NCT03834740	Glioblastoma Multiforme Brain Gliomas	24	Ribociclib, Everolimus	1	Recruiting	USA
46	NCT03224104	Astrocytoma, Grade III Glioblastoma	81	Zotiraciclib, Temozolomide, Radiotherapy	1	Recruiting	SW
47	NCT02942264	Brain Tumors Astrocytoma, Astroglioma Glioblastoma Gliosarcoma	152	Zotiraciclib, Temozolomide	1, 2	Recruiting	USA
48	NCT02073994	Cholangiocarcinoma Chondrosarcoma Glioma Other Advanced Solid Tumors	170	Ivosidenib	1	Active, not recruiting	USA, FR
49	NCT02481154	Glioma	150	Vorasidenib	1	Active, not recruiting	USA
50	NCT00884741	Glioblastoma Multiforme Gliosarcoma Supratentorial Glioblastoma	637	Bevacizumab, Temozolomide, Radiotherapy	3	Completed	USA
51	NCT00731731	Adult Glioblastoma	125	Temozolomide, Vorinostat	1, 2	Active, not recruiting	USA
52	NCT00128700	Brain and Central Nervous System Tumors	20	Temozolomide, Vatalanib, Radiotherapy	1, 2	Completed	BE, DE, IT, NL, SW
53	NCT00108056	Glioma	26	Enzastaurin	1	Terminated	USA
54	NCT00190723	Malignant Glioma	120	Enzastaurin	2	Completed	USA
55	NCT00503724	Brain and Central Nervous System Tumors Neuroblastoma	32	Enzastaurin	1	Completed	USA
56	NCT00006247	Brain and Central Nervous System Tumors	33	Semaxanib	1	Terminated	USA
57	NCT01229644	Glioma	10	Crenolanib	2	Terminated	USA
58	NCT01393912	Diffuse Intrinsic Pontine Glioma Progressive or Refractory High-Grade Glioma	55	Crenolanib	1	Completed	USA

#	ClinicalTrials.gov Identifier	Conditions	# of Patients Enrollment	Interventions	Study Phase	Status	Locations
59	NCT00305656	Adult Giant Cell Glioblastoma	31	Cediranib	2	Completed	USA
		Adult Glioblastoma					
		Adult Gliosarcoma					
		Recurrent Adult Brain Tumor					
60	NCT00326664	Recurrent Glioblastoma	55	Cediranib	1	Completed	USA
61	NCT00503204	Brain Tumor	20	Cediranib, Lomustine	1	Completed	USA, UK
62	NCT00704288	Glioblastoma Multifforme	222	Cabozantinib	2	Completed	USA
63	NCT00960492	Glioblastoma Multifforme	26	Cabozantinib, Temozolomide, Radiotherapy	1	Completed	USA
		Gliosarcoma					
64	NCT00337207	Brain and Central Nervous System Tumors	55	Bevacizumab	2	Completed	USA
65	NCT01740258	Malignant Glioma	69	Bevacizumab, Temozolomide, Radiotherapy	2	Completed	USA
		Grade IV Malignant Glioma					
		Glioblastoma					
		Gliosarcoma					
66	NCT00271609	Recurrent High-Grade Gliomas	88	Bevacizumab	2	Completed	USA
		Malignant Gliomas					
67	NCT01290939	Glioblastoma Multifforme	433	Bevacizumab, Lomustine	3	Unknown	USA
		Cognition Disorders					
		Disability Evaluation					
68	NCT01860638	Glioblastoma Multifforme	296	Bevacizumab, Lomustine	2	Completed	AU
69	NCT00884741	Glioblastoma Multifforme	637	Bevacizumab, Chemiotherapy, Radiotherapy	3	Completed	USA
		GliosarcomaSupratentorial					
70	NCT00943826	Glioblastoma Multifforme	921	Bevacizumab, Temozolomide, Radiotherapy	3	Completed	USA
71	NCT00895180	Adult Glioblastoma Multifforme	80	Olaratumab, Ramucirumab	2	Completed	USA
72	NCT00369590	Adult Anaplastic Astrocytoma	58	Aflibercept	2	Completed	USA
		Adult Anaplastic Oligodendroglioma					
		Adult Giant Cell Glioblastoma					
		Adult Gliosarcoma					
		Recurrent Adult Brain Tumor					
73	NCT00093964	Glioblastoma Multifforme	81	Cilengitide	2	Completed	USA

#	ClinicalTrials.gov Identifier	Conditions	# of Patients Enrollment	Interventions	Study Phase	Status	Locations
74	NCT00085254	Adult Giant Cell Glioblastoma	112	Cilengitide, Temozolomide, Radiotherapy	1, 2	Completed	USA
		Adult Glioblastoma					
		Adult Gliosarcoma					
75	NCT00689221	Glioblastoma Multiforme	545	Cilengitide, Temozolomide, Radiotherapy	3	Completed	USA, DE
76	NCT00165477	Glioblastoma Multiforme	23	Lenalidomide, Radiotherapy	2	Completed	USA
		Gliosarcoma					
		Malignant Gliomas					
77	NCT03345095	Newly Diagnosed Glioblastoma	750	Marizomib, Temozolomide, Radiotherapy	3	Recruiting	AU, BE
78	NCT00006773	Adult Anaplastic Astrocytoma	42	Bortezomib	1	Terminated	USA
		Adult Anaplastic Oligodendroglioma					
		Adult Giant Cell Glioblastoma					
		Adult Glioblastoma					
		Adult Gliosarcoma					
		Recurrent Adult Brain Tumor					
79	NCT00998010	Brain and Central Nervous System Tumors	25	Bortezomib, Temozolomide, Radiotherapy	2	Completed	USA

AU: Austria; BE: Belgium; CA: Canada; DE: Germany; DK: Denmark; ES: Spain; FR: France; IT: Italy; NL: Netherlands; SW: Switzerland; UK: United Kingdom; USA: United States of America

majority of approaches are directed against signaling pathways related to cell proliferation and glioma invasion, angiogenesis and inhibition of apoptosis.²²⁻²⁵ Table 2 reports the classification of the target therapies used for malignant brain tumors (Table 2).

2.1. Tyrosine Kinase Inhibitors

Tyrosine kinase receptors consist in an extracellular ligand-binding and a transmembrane tyrosine kinase domain containing sites for autophosphorylation. Upon the binding of its ligand, the receptors undergo dimerization and phosphorylation of specific tyrosines, those become binding sites, recruit proteins and activate downstream intracellular pathways, ultimately resulting in tumor maintenance and proliferation.²⁶⁻²⁸

The most widely studied tyrosine kinase receptors are the epidermal growth factor receptor (EGFR), the platelet-derived growth receptor (PDGFR), the fibroblast growth factor receptor (FGFR) and the hepatocyte growth factor receptor (HGFR). All of them are constantly overexpressed or mutated in GBMs. Tyrosine kinase inhibitors (TKIs) are molecules which bind the aforementioned receptors, blocking their downstream signals.

2.1.1 EGFR

The EGFR gene is amplified or overexpressed in 40% to 60% of the primary GBMs, whereas loss of exons 2 to 7 (EGFRvIII) is present in 40-50% of the cases.²⁹⁻³¹

Table 2. Classification of Target Therapies for Malignant Brain Tumors

Target Therapy		
Candidate Drugs	Target	Biological Role in GBM
TKIs	EGFRvIII	Proliferation, migration, invasion, and resistance to apoptosis
	PDGFR	
	FGFR	
	HGFR	
PI3K/AKT/mTOR Is	PI3K	Growth, metabolism, proliferation, migration
	AKT	
	mTORC1	
FTIs	RAS/MAPK	Cell cycle maintenance and proliferation
	BRAF V600E	
p53Is	MDM2/MDM4	Cell cycle progression and resistance to apoptosis
pRBIs	CDK4/CDK6	
IDHIs	IDH1	Metabolism, proliferation, invasion, angiogenesis
HDACIs	Histones	Dysregulation DNA transcription, expansion of gene mutations
AIs	VEGF-A	Blood vessel formation, proliferation, therapeutic resistance
	VEGFR1	
	PKC	Tumor microenvironment maintenance
IIs	Integrins	Cell adhesion, migration, metastasis
PIs	Proteasome complex	Homeostasis, growth and resistance to apoptosis

AIs: Angiogenesis Inhibitors; EGFR: Epidermal Growth Factor Receptor; FGFR: Fibroblast Growth Factor Receptor; FTIs: Farnesyl Transferase Inhibitors; HDACIs: Histone Deacetylases Inhibitors; HGFR: Hepatocyte Growth Factor Receptor; IDH1: Isocitrate Dehydrogenase 1; IDHIs: Isocitrate Dehydrogenase Inhibitors; IIs: Integrin Inhibitors; mTOR: Mammalian Target of Rapamycin; mTORC1: Mammalian Target of Rapamycin Complex 1; PDGFR: Platelet-Derived Growth Receptor; PI3K: Phosphatidylinositol 4,5-Bisphosphate-3; PIs: Proteasome Inhibitors; PKC: Protein Kinase C; TKIs: Tyrosine Kinase Inhibitors; VEGF-A: Vascular Endothelial Growth Factor A; VEGFR1: Vascular Endothelial Growth Factor Receptor 1

EGFRvIII mutation leads to a ligand-independent kinase activity and, accordingly, an EGFR-pathway overactivation, resulting in increased cell proliferation, invasiveness and resistance to chemotherapeutic agents.^{32, 33} Gefinitib (Iressa®) and erlotinib (Tarceva®) are approved TKIs directed against EGFRvI-II. Three phase II clinical trials (#NCT00025675, #NCT00238797, #NCT00016991) highlighted the efficacy of gefinitib, pointing out a progression-free survival at 6 months (PFS-6) of 13%.³⁴ Erlotinib lacked success as a monotherapy, but enhanced the efficacy of chemo-radiotherapy, especially if associated with temozolomide (TMZ) and carmustine at a dose of 150 or 300 mg/daily.^{35, 36} Similar results have been reported for lapatinib, afatinib and dacomitinib.³⁷

In addition, two monoclonal antibodies (MAbs) are under observation. Cetuximab, a chimeric murine-human IgG1 Mab that binds the extracellular EGFR domain inducing tumor apoptosis.³⁸ As a monotherapy, it demonstrated a PFS-6 of 9.2% and an increased overall survival (OS) of 5 months. In combination with bevacizumab and irinotecan cetuximab, it showed a PFS-6 of 30% and a median OS of 7.2 months.³⁹ ABT-414, an EGFR-directed MAb conjugated to an anti-microtubulin agent, had a PFS-6 of 28.3% in monotherapy or when combined with standard temozolomide chemoradiotherapy (#NCT02573324).⁴⁰

2.1.2. PDGFR

PDGFR gene amplification is found in nearly 15% of GBMs, and the receptor's overexpression, which leads to tumor growth and angiogenesis, is frequently associated with transition from low- to high-grade glioma.³⁰ Imatinib is the most famous PDGFR inhibitor, used in many hematological tumors for its activity against the mast/stem cell growth factor receptor (c-KIT), and oncogene fusion protein BCR-ABL.

Many phase II clinical trials have proven that imatinib monotherapy failed to improve PFS-6 or OS in patients with GBM,⁴¹ but resulted in a good response in combination with hydroxyurea.⁴²

Sorafenib, vandetanib, dasatinib and bosutinib are other PDGFR inhibitors. However, many clinical trials have failed to demonstrate the efficacy of dasatinib,

both as monotherapy and combined with radiotherapy, TMZ and lomustine.^{43,44}

2.1.3. *FGFR*

Erdaftinib, a selective FGFR TKI, showed promising results in patients with GBM harboring oncogenic FGFR-TACC fusion.^{45,46}

2.1.4. *HGFR/c-MET*

HGFR, also known as c-Met, amplification/mutation has a role in promoting gliomagenesis and drug resistance.^{47,48} Crizotinib, specifically designed against c-Met, has given some results in combination with dasatinib.^{49,50} Analogous results have been reported for SGX523^{51,52} (#NCT00606879, #NCT00607399). Conversely, onartuzumab and rilotumumab (AMG102) basically demonstrated no clinical benefits.^{53,54} Two phase II clinical trials have been completed, one with AMG102 as monotherapy (#NCT00427440), and the other with AMG102 plus bevacizumab (#NCT01113398), both for patients with recurrent high-grade gliomas.

2.2. *PI3K/AKT/mTOR Inhibitors*

The Cancer Genome Atlas analysis highlighted the presence of PI3K/AKT/ mTOR signaling pathway dysregulation in 50-60% of GBMs.^{55,56} The activation of phosphatidylinositol 4,5-bisphosphate-3 (PI3K) regulates the activity of many kinase proteins, such as AKT. It transduces the signals to many downstream intracellular effectors, like the mammalian target of rapamycin (mTOR). A fundamental intracellular protein is mTOR, involved in cell growth signaling and tumorigenesis. It is composed of two subunits, mTORC1-2, with different roles, and mTORC1, particularly involved in the transition of the cell cycle from G1 to S. The Food and Drug Administration (FDA) approved three mTORC1 inhibitors: sirolimus (Rapamycin, Rapamune®), everolimus® and temsirolimus®.

Temsirolimus has been evaluated in some significant clinical trials; one of these was a phase II study involving 65 patients with recurrent GBM. It

demonstrated a radiographic improvement in 36% of the patients, a PFS-6 of 7.8% and median OS of 4.4 months.⁵⁷

Sirolimus has been tested in combination with surgery (#NCT00047073), gefitinib in 34 recurrent glioma patients, and erlotinib (#NCT00672243), demonstrating moderate effectiveness.⁵⁸

Everolimus was studied in combination with gefitinib (#NCT00085566), bevacizumab or chemioradiotherapy. A phase II clinical trial tested the combination of everolimus, TMZ and radiotherapy versus conventional standard of care (#NCT00553150).

However, mTOR inhibitors have not demonstrated significant clinical activity, if not in combination with other treatments. This is due to their selectivity for mTORC1 and not mTORC2, ensuring only a partial blocking of the mTOR function.

In fact, two novel ATP-competitive mTORC2 inhibitors (CC214-1 and CC214-2) are under investigation, in order to overcome the resistance of mTOR inhibitors.⁵⁹

Other promising strategies involve the selective PI3K inhibitor, buparlisib, which has an antitumor activity, especially when associated with bevacizumab in patients with recurrent GBM.⁵⁹

Perifosine is a novel selective AKT inhibitor, currently tested in some ongoing trials. A phase II study investigated perifosine as a monotherapy for recurrent malignant gliomas⁶⁰ (#NCT00590954).

2.3. *Farnesyl Transferase Inhibitors*

Following the activation of TK receptors, the intracellular RAS protein family undergoes post-translational modifications and triggers multiple effector pathways, including the RAF and MAP kinases (MAPK) involved in cell proliferation, differentiation and survival.

However, translocation of RAS to the cell membrane requires a post-translational alteration catalyzed by the farnesyl transferase enzyme.^{30,61}

Farnesylation is the limiting step in RAS activities and the specific farnesyl transferase inhibitors (FTIs) lock all its functions upstream, and consequently the intracellular RAS-RAF-MEK-MAPK pathway.⁶²

Among these, tipifarnib (Zarnestra®), exhibited in a phase II trial, had modest efficacy as a monotherapy or after radiotherapy, in patients with newly diagnosed and recurrent malignant gliomas.^{63,64}

Lonafarnib, an FTI, was tested in a phase I clinical trial in combination with TMZ and radiotherapy, with promising results⁶⁵ (#NCT00049387).

2.3.1. *BRAF V600E*

RAF kinases, also triggered by the RAS system, are involved in intracellular growth pathways and stimulation.

Several studies reported the presence of BRAF V600E mutation, especially in infant gliomas.⁶⁶ Vemurafenib, a BRAF inhibitor, is under investigation in a phase I ongoing trial, for children with recurrent BRAFV600E-Mutant gliomas⁶⁷ (#NCT01748149).

2.4. *MDM2/MDM4/p53 inhibitors*

The dysregulation of p53 signaling pathways is found in more than 80% of high-grade gliomas. The p53 is fundamental in cell-cycle arrest and apoptosis; mutation results in clonal expansion of tumor cells and genetic instability.^{68,69}

In 20% of the patients, the p53 inactivity is due to the MDM2 or MDM4 overexpression. MDM2/MDM4 inactivates p53 and consequently leads to loss of cancer suppression.^{30,70}

Therefore, an effective strategy rationale is to restore the p53 activity, by molecules targeting MDM2 or MDM4. Preclinical studies demonstrated the successful suppression of GBM growth with several MDM2 inhibitors, including RG7112,⁷¹ RG7388 and AMG232 as well as many others in progress (#NCT03107780).

2.5. *CDK4/CDK6/pRB inhibitors*

The altered function of retinoblastoma protein (pRB) contributes to gliomagenesis in 78% of the cases and the overexpression of CDK4/CDK6 plays a fundamental role in the modulation of this pathway, involved in cell growth.⁷²⁻⁷⁴

Novel agents directed to CDK4 and CDK6 demonstrated strong antitumor efficacy in RB1-wild-type GBM, such as ribociclib and palbociclib.

Ribociclib was tested in a phase I trial for recurrent glioblastoma or anaplastic glioma⁷⁵ (#NCT02345824); palbociclib was employed as a monotherapy for brain metastases⁷⁶ (#NCT02896335).

Zotiraclib, a multi-CDK inhibitor, has been explored in clinical trials for newly diagnosed or recurrent gliomas (#NCT02942264, #NCT03224104).

2.6. *Isocitrate dehydrogenase-1 inhibitors*

Isocitrate dehydrogenase-1 (IDH1) mutation is one of the most frequent abnormalities found in high-grade gliomas, and according to the World Health Organization, is a new classification of brain tumors also having predictive value of treatment response. This mutation consists in the gain-of-function with the production of D-2-hydroxyglutarate, which interferes with cellular metabolism^{77,78}. Ivosidenib, an IDH1 inhibitor, is being evaluated in a phase I ongoing trial, as a monotherapy, for advanced solid tumors including IDH-mutated gliomas (#NCT02073994).

2.7. *Histone deacetylases inhibitors*

Histone deacetylases (HDAC) are enzymes involved in the regulation of histones, which are proteins that organize the DNA structure and regulate gene transcription.

HDAC inhibitors have an emerging role in the treatment of GBMs, potentially promoting the apoptosis of the cancer cells.⁷⁹

Vorinostat, an oral quinolone HDAC inhibitor, is being studied in phase I/II clinical trials, as a monotherapy in recurrent GBM,⁸⁰ and in combination with TMZ, showing good tolerance and giving promising results⁸¹ (#NCT00731731).

Panobinostat, Romidepsin and other HDAC inhibitors are still under evaluation.

2.8. *Angiogenesis inhibitors*

The tumor's microenvironment, together with pathological angiogenesis and neovascularization, play

a fundamental role in the development and progression of high-grade gliomas.

Acting as managers for the angiogenesis process, as well as for a wide range of CNS vascular pathologies, they are mainly vascular growth factors of all the vascular endothelial growth factor-A (VEGF-A) and its receptors, VEGFR1 and VEGFR2, found on the glioma's endothelial cells.⁸²⁻⁸⁵

Efforts to downregulate this pathway have been pursued through the development of agents directed to VEGF/VEGFR, which not only block neoangiogenesis, but also have an effect on the vascular phenotype.

The inhibition of VEGF signaling also changes the vessels' diameter, permeability and tortuosity, decreasing tumor hypoxia and consequently disrupting the survival mechanism in glioma cells as well as increasing chemotherapy delivery and radiosensitivity.⁸³⁻⁸⁵

2.8.1. VEGFR

Several studies evaluated VEGFR inhibitors for patients with newly diagnosed, as well as recurrent GBM.

Vatalanib has been tested in phase I/II studies in combination with TMZ and radiotherapy (#NCT00128700). Cediranib demonstrated no clinical benefits in a phase II clinical trial as a monotherapy (#NCT00305656), yet there was greater benefit together with lomustine in a randomized phase III study⁸⁶ (#NCT00503204).

Cabozantinib is a promising agent against VEGFR and MET signaling, evaluated in two phase II studies involving newly diagnosed (#NCT00960492) and recurrent GBM (#NCT00704288). Ramucirumab and icrucumab are new MAb's under evaluation, directed to VEGFR-2 and VEGFR-1, respectively.⁸⁷

2.8.2. VEGF

The most relevant of the VEGF inhibitors is bevacizumab, a humanized IgG1 monoclonal antibody against VEGF-A, which in 2009 received FDA-approval for the treatment of recurrent GBM, after the high radiographic response rates (ranging from 28% to 59%) achieved in two clinical trials.^{88,89}

The significant antitumor potential of bevacizumab has been proven in many studies, using it as a monotherapy or in combination with lomustine (#NCT01290939) and radiochemotherapy.^{90,91}

Combinations of bevacizumab with the standard of care were examined in two phase III clinical trials, AVAglio⁹² (#NCT00943826) and RTOG-0825⁹³ (#NCT00884741), and although both demonstrated encouraging results in PFS survival benefit, bevacizumab remains only an alternative treatment in the recurrent setting.

Another promising agent is aflibercept, known as VEGF-trap, a recombinant product fusion protein which has been studied in phase II trials with a PFS-6 of 7.7% and median OS of 3 months.^{94,95}

2.8.3. Protein kinase C

Protein kinase C (PKC) is implicated in activation of the angiogenesis process, cell proliferation and constitution of the microenvironment, therefore, it is a potentially attractive therapeutic target.

Enzastaurin, a potent PKC inhibitor, demonstrated in a phase I/II trial a 25% radiographic response and a PFS-6 of 7% in GBM.⁹⁶

Tamoxifen, a modulator of the estrogen receptor, has been described as a PKC inhibitor and was tested in GBM therapy with a median OS of 9.7 months.^{97,98}

2.9. Integrin inhibitors

The integrins are transmembrane proteins which bind multiple extracellular ligands and mediate cell adhesion and migration. They are expressed at a high level in malignant glioma cells and play a central role in the angiogenesis, development, invasion and metastasis of the tumor.^{99,100} Integrin inhibitors are being investigated as a means of reducing this mechanism.

Cilengitide, which competitively inhibits integrin ligand binding,¹⁰¹ has been evaluated in a phase I/II study stand-alone;¹⁰² or in a phase III trial, associated to TMZ and radiotherapy, resulting in a good improvement of PFS-6¹⁰³ (#NCT00689221).

Thalidomide and lenalidomide, which interfere with the expression of integrin receptors and have an

antiangiogenic effect, are being studied for GBM therapy, with results that are still unsatisfactory.¹⁰⁴⁻¹⁰⁶

2.10. Proteasome inhibitors

Proteasomes are proteins with enzymatic activities involved in the regulation of homeostasis, cell growth and apoptosis.

Bortezomib (Velcade®), the most used proteasome inhibitor in the oncological field, has also been tested for GBM therapy in combination with chemio-radiotherapy¹⁰⁷ (#NCT00006773).

The pan-proteasome inhibitor, Marizomib, is currently undergoing phase III evaluation in newly diagnosed GBMs¹⁰⁸ (#NCT03345095).

Discussion

The present literature review highlights the current role of a series of target therapies, especially tyrosine kinase and angiogenesis inhibitors, in the treatment of malignant CNS tumors.

Several steps forward have been done in the recent years toward a deep understanding of complex pathophysiologic pathways associated with a wide spectrum of neurological and neuro-oncological pathologies of adulthood and pediatric age.¹⁰⁹⁻¹¹¹ Nevertheless, the lack of success of the standard of care and the still largely dismal prognosis of patients affected by high-grade gliomas dictate the urgent need of new and more effective therapeutic approaches.

In this scenario, the improved understanding of genome mutations underlying the GBM phenotype has led to greater insight into the biology of the tumor, at the same time providing the opportunity for designing novel and personalized treatment strategies.^{82, 112, 113}

Data from the Cancer Genome Atlas project⁵⁵ revealed the complicated genetic profile of GBMs and recognized the core signaling and transduction pathways commonly involved in the growth, proliferation, angiogenesis and spreading of the tumor.¹¹⁴

A further tangible aspect of these advances is the latest World Health Organization's classification of brain tumors, which integrates data from traditional histological analysis with biomolecular connotation obtained by specific genetic analysis and characterizations.¹¹⁵

Accordingly, the target therapies developed on the basis of the above have detected molecular abnormalities, and have made use of pharmacological agents tailored to specific mutations, specific to tumor subtypes.

Typical genetic alterations of GBMs are the over-expression of the tyrosine kinase receptors, especially the EGFR, PDGFR, FGFR and HGFR, dysregulation of PI3K/AKT/mTOR and RAS/MAPK pathways, as well as p53 or pRB mutations.^{30, 116, 117}

TKIs have long been investigated in several clinical trials with disappointing results. Despite the extreme specificity of these agents, they were not efficacious as a monotherapy, thus the current approach consists in the combination of multiple molecular agents within the same targets or between separate pathways.^{33, 118, 119}

PI3K/AKT/mTOR pathway and farnesyltransferase inhibitors show low tolerability and safe profiles during clinical studies, but have a synergistic effect only in combination with standard of care.^{58, 120}

Likewise, agents directed at restoring p53 and pRB activity gave encouraging results in association with chemotherapy and whole brain radiotherapy.^{76, 121} The newly discovered alterations in metabolic pathways, including IDH1 and HDAC enzymes, seem to be up-and-coming targets. Currently, anti-angiogenic drugs are among the most promising. They focused on the blocking of VEGF/VEGFR,^{122, 123} along with components of the tumor microenvironment, such as protein kinase C, integrins and proteasome complexes.^{89, 124, 125}

Despite the rationale of the target therapies, the vast intratumoral heterogeneity and GBM cell plasticity have caused a rapid shift toward resistant tumor phenotypes, the latter responsible for the failure of the therapy.¹²⁶⁻¹²⁸

Additionally, the route of drug administration still presents a limitation for the efficacy of these therapies. Recent progress has been made through the use of stereotactic or endoscopic techniques for the intrathecal administration of pharmacological agents directly into the tumor site, also benefiting from the minimal invasiveness of these approaches, well evident also for other neurosurgical pathologies.¹²⁹⁻¹³¹

Last but not least, the immunological tumor microenvironment, composed of glia cells and lymphocytes, consistently modulates tumor sensitivity to treatment.¹³²⁻¹³⁴

Conclusion

The improved knowledge of the biology of tumors has recently made it possible to transform the molecular alterations at the base of the high malignancy of GBM, into different treatment strategies.

Good results came from tyrosine kinase inhibitors, primarily erlotinib and gefitinib. Similarly, PI3K/AKT/mTOR inhibitors and p53 restoring agents proved their efficacy in several clinical trials. Bevacizumab, in association with TMZ and radiotherapy, has been approved for recurrent GBMs.

An in-depth identification of driver molecular alterations may make it possible to appropriately select those patients who are candidates for a target therapy.

The greatest challenge of the near future consists in overcoming the issue of escape of GBM that is present in all of these therapies.

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