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Glioma: an overview of current classifications, characteristics, molecular biology and target therapies

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TABLE OF CONTENTS

1. ABSTRACT

Glioma is the most common primary brain tumor, accounting for 30% to 40% of all intracranial tumors. About half of all gliomas in adults are glioblastomas. Patients with glioblastoma have a poor prognosis, with a median survival of one year despite aggressive therapy and a five year mortality of over 95%. Although considerable progress has been made in the technical proficiencies of surgical and radiation oncology, the overall impact of these advances on clinical outcomes has been disappointing. Recent elucidation of several biochemical and molecular markers associated with glioma may provide valuable insight into the underlying biological features of the disease, as well as illuminate possible new therapeutic targets. This review focuses on the current characteristics, classifications, and management of glioma.

2. INTRODUCTION

Glioma, a type of tumor arising from glial cells, is the most common primary tumor of the central nervous system (CNS), including brain and spine (1-3). The most common site of gliomas is the brain. Gliomas make up about 30% of all brain and CNS tumors and 80% of all malignant brain tumors (1-3). The incidence of glioma is reported to be more frequently seen in male patients than in female patients, with a rate of 7.1.4 per 100,000 male population and 5.0.6 per 100,000 female population (4-7). In general, signs and symptoms of glioma include headache, nausea and vomiting, seizures, visual loss, pain, cranial nerve disorders, weakness, and numbness; symptoms vary from person to person depending on the location of the glioma (8, 9). It has been well established that the development of gliomas may be attributed to the interactions between environmental and genetic factors. Major environmental risk factors include electromagnetic radiation from cell phones, alcohol consumption, infectious agents, allergic conditions, and smoking, which can all significantly contribute to the development of glioma (10-12). Besides the factors mentioned, genetic factors may also be implicated in the pathogenesis of glioma. For example, mutations in isocitrate dehydrogenase (IDH) 1or IDH2 are linked to the occurrence of glioma (13, 14). On basis of these findings, several strategies have been applied in glioma treatment. The current review will focus on the clinical characteristics, pathogenesis, and management of glioma.

3. EPIDEMIOLOGY OF GLIOMA

Gliomas typically occur during middle age, with a peak incidence between 40 and 65 years (15). Gliomas comprise more than 80% of all brain tumors; therefore, descriptive epidemiology regarding glioma often is framed in the broader context of brain tumors as a whole. Overall, brain tumors are relative rare events. The incidence of primary brain tumors in the United States is estimated to be 10 per 100,000 persons per year, in a male-female ratio of 6:4 (16, 17). As compared to other countries, The United States has higher incidences of primary brain tumors, with 22,000 new cases and 13,000 deaths annually. Less developed countries (e.g., African nations, Pacific islanders) tend to report lower rates of death caused by gliomas than more developed countries (e.g., United States, Australia, and Europe), primarily due to environmental factors such as electromagnetic radiation from cell phones and alcohol consumption.

4. THE CLASSIFICATION OF GLIOMAS

4.1. The classification of gliomas by cell type

Most primary brain tumors are of neuroepithelial origin, of which gliomas constitute the largest subgroup. Glial cells comprise ~70% of the total cell population in the nervous system, and can be broadly classified as micro- and microglia (21, 22). Microglia, which constitute 5–10% of the glial population, are macrophage-like cells (23-25). Microglia can be either neuroectoderm-derived oliogodendrocytes, which produce myelin to enshealth neuronal axons, or astrocytes, which are 40–50% of all glia and are therefore the most abundant glia type in terms of number and volume (26-28). Under normal conditions, microglia and astrocytes are quiescent; they are activated in response to injury or in disease states, and contribute to the pathogenesis of neurological disorders (26-28). It is thought that gliomas are tumors of neuroepithelial tissue and are currently classified on the basis of morphological appearance: astrocytic, oligodendroglial, ependymal and choroid plexus tumors. Astrocytomas, which are tumors composed predominantly of neoplastic astrocytes, amount to 80 – 85% of all gliomas. The average age at diagnosis is 30-40 years (29, 30). Astrocytomas cause regional effects by compression, invasion and destruction of brain parenchyma, arterial and venous hypoxia, competition for nutrients, release of metabolic end products, and release and recruitment of cellular mediators that disrupt normal parenchymal functions (31). Oligodendrogliomas occur primarily in adults (9.4.% of all primary brain and CNS tumors) but are also found in children (4% of all primary brain tumors). The average age at diagnosis is 35 years (32, 33). The first symptom of an oligodendroglioma is the onset of seizure activity. They occur mainly in the frontal lobe. Headaches combined with increased intracranial pressure are also a common symptom of oligodendroglioma (34). Depending on the location of the tumor, multiple neurological deficits may be appreciated, ranging from visual loss, motor weakness and cognitive decline. Ependymomas are tumors that arise from the ependyma and are among the most challenging childhood brain tumors (35). Although 50-70% of ependymomas are cured with surgery and irradiation, a significant percentage of tumors recur. Ependymomas make up about 5% of adult intracranial gliomas and up to 10% of childhood tumors of the CNS. Their occurrence seems to peak at age five years and then again at age 35 (35). Ependymomas are composed of cells with regular, round to oval nuclei. There is a variably dense fibrillary background. Tumor cells may form gland-like round or elongated structures that resemble the embryologic ependymal canal, with long, delicate processes extending into the lumen; more frequently present are perivascular pseudorosettes in which tumor cells are arranged around vessels with an intervening zone consisting of thin ependymal processes directed toward the wall of the vessel (36). The choroid plexus tumors are rare tumors of neuro ectodermal origin, accounting for less than 1% of intracranial tumors in all ages. Most cases present in children are less than two years old in age. These tumors have been classified according to histopathological criteria into papilloma and carcinoma. Choroid plexus tumors may present with overt intracranial hypertension with or without focal neurological signs. In the adult population, headaches are the most commonly encountered symptom (37, 38).

4.2. The classification of gliomas by grade

Gliomas are graded by pathologic evaluation of the tumor (39). Grading is described by World Health Organization (WHO) consensus criteria, in which four classes are described, on the basis of hallmarks of the tumor histological aberrations: nuclear atypia, mitotic activity, endothelial hyperplasia and necrosis (40-42). Grade I tumors are biologically benign and excision that leads to recovery; Grade II tumors are low-grade malignancies that may follow long clinical courses, but early diffuse infiltration of the surrounding brain renders them often not totally resectable. It has been described that up to 70% of Grade II gliomas progress to Grade III/IV Astrocytomas within 5–10 years from diagnosis; Grade III tumors exhibit aggressive behaviour characterized by increased anaplasia and mitosisas compared to Grade II tumors; accordingly Grade III tumors have often a quick progression. Grade IV tumors, also known as glioblastoma multiforme (GBM), exhibit more advanced features of malignancy, including vascular proliferation and necrosis (two to five times higher than Grade III tumors) and are often refractory to radiotherapy or chemotherapy (43). A characteristic of GBM is the ability to infiltrate and invade the surrounding non-tumoral brain tissue. Patients with GBM have a poor prognosis, with a median survival of one year despite aggressive therapy; five-year mortality is greater than 95% (44, 45). GBMs are further subdivided into primary or secondary GBM subtypes according to their clinical features. Primary GBMs account for

the great majority of GBM cases in elderly patients, whereas secondary GBMs are quite rare and tend to occur in younger patients (often younger than 45 years). Primary GBM presents ex novo, with no evidence of prior symptoms or pre-existent low grade glioma (Grade I and Grade II). Secondary GBMs are most often the result of progressive transformation of lower grade astrocytomas in malignant neoplasms (44, 45).

In conclusion, low-grade gliomas grow slowly, commonly over many years, and can be followed without treatment unless the tumors continue to grow and/or become symptomatic. High-grade gliomas (Grade III and Grade IV) are highly vascular tumors and have a tendency to infiltrate (40-42). They have extensive areas of necrosis and hypoxia, often with local destruction of the blood-brain barrier. As a rule, high-grade gliomas almost always recur even after complete surgical excision.

4.3. Classification of gliomas by location

Gliomas can be classified according to whether they are above or below the tentorium cerebelli. The tentorium cerebelli is an extension of the dura mater that separates the cerebrum (above) from the cerebellum (below). Accordingly gliomas are classified as being supratentorial (46), infratentorial (47) and pontine (48). Supratentorial gliomas are mostly found in adults (70%) (46). Infratentorial gliomas are mostly found in children (70%) (47). Pontine gliomas are located in the pons of the brainstem (48) and run the risk of interfering with the critical functions of the pons, such as breathing. Pontine gliomas are usually high-grade, locally infiltrative, and with a uniformly poor prognosis.

5. GENETIC ALTERATION OF GLIOMAS

The exact etiologies of gliomas are not known. There are a few known hereditary genetic disorders that predispose their development. Two of the most common disorders are neurofibromatoses (NF) types one and two and tuberous sclerosis complex (TSC) (49-51). NF is an inherited neurocutaneous disease that has a major impact on the nervous system, eye, skin, and bone. Individuals with NF-1 have a predisposition to benign and malignant tumor formation and the hallmark lesion is the neurofibroma, a benign peripheral nerve sheath tumor (52). TSC causes abnormal cellular differentiation and proliferation along with abnormal neuronal migration. It affects the brain (cortical and subcortical tubers, subependymal nodules, and giant cell astrocytomas), the kidney (angiomyolipomas, cysts, carcinomas), skin (hypomelanotic macules, shagreen patches, facial angiofibromas, periungual fibromas), eye (retinal hamartomas), heart (rhabdomyomas), and, to a lesser extent, other organs (53).

In terms of the development of gliomas, different oncogenes can cooperate in the pathogenesis of gliomas, most of which are related with DNA damage repair. DNA damage is a likely major cause of progression to cancer. Excess DNA damage can give rise to mutations through translation synthesis. Furthermore, incomplete DNA repair can give rise to epigenetic alterations or epimutations. Such mutations and epimutations may provide a cell with a proliferative advantage, which can then, by a process of natural selection, lead to progression to cancer (54, 55). Germ-line (inherited) polymorphisms of the DNA repair genes excision repair cross complementation 1(ERCC1), ERCC2 and X-ray repair complementing defective repair in Chinese hamster cells 1 have been shown to increase the risk of glioma (56, 57). The finding indicates that altered or deficient repair of DNA damage contributes to the formation of gliomas.

Several acquired (not inherited) genetic mutations have been found in gliomas as well. The most common genetic alterations detected in gliomas are tumor suppressor protein 53 (p53) mutations, murine double mimut (MDM) 2 amplification, loss of heterozygosity at 10q, phosphatase and tensin homolog (PTEN) mutation, and epidermal growth factor receptor (EGFR) amplification/overexpression, along with EGFRvIII expression, p16/p14 co-deletion, loss of 1p/19q, and telomerase re-activation (Figure 1).

5.1. P53 signaling pathway

p53 is the “guardian of the genome”, which is responsible for ensuring that DNA is copied correctly and destroys the cell (apoptosis) during DNA and cell duplication, if the DNA is mutated and can’t be fixed. The p53 signaling pathway is activated in response to a variety of stress signals, allowing p53 to coordinate transcription programs that ultimately contribute to tumor suppression. Loss of p53 function, through mutations in p53 itself or perturbations in pathways signaling to p53, is a common feature in the majority of human cancers (58). p53 is often mutated early in gliomas. A nearly universal feature of secondary GBM is the loss of function of the p53 pathway. It is through either point mutations that prevent DNA binding or loss of chromosome 17p, which is a frequent and early event in the pathological progression of secondary GBM (59). In addition, amplification of the p53 antagonists MDM2 and MDM4 have been found in distinct subsets of p53 intact GBMs, as well as mutations and/or deletions in the CDKN2A second locus that encodes p14ARF (which is a regulator of p53 (60-62)). The importance of p53 in gliomagenesis is also demonstrated by the increased incidence of gliomas in Li-Fraumeni syndrome, which is characterized by germline p53 mutations (63).

5.2. PTEN

PTEN is a dual lipid and protein phosphatase that dephosphorylates the lipid phosphatidylinositol-3,4,5-triphosphate (PIP3), which is the product of phosphatidylinositol-3 kinase (PI3K) (64). Upon activation

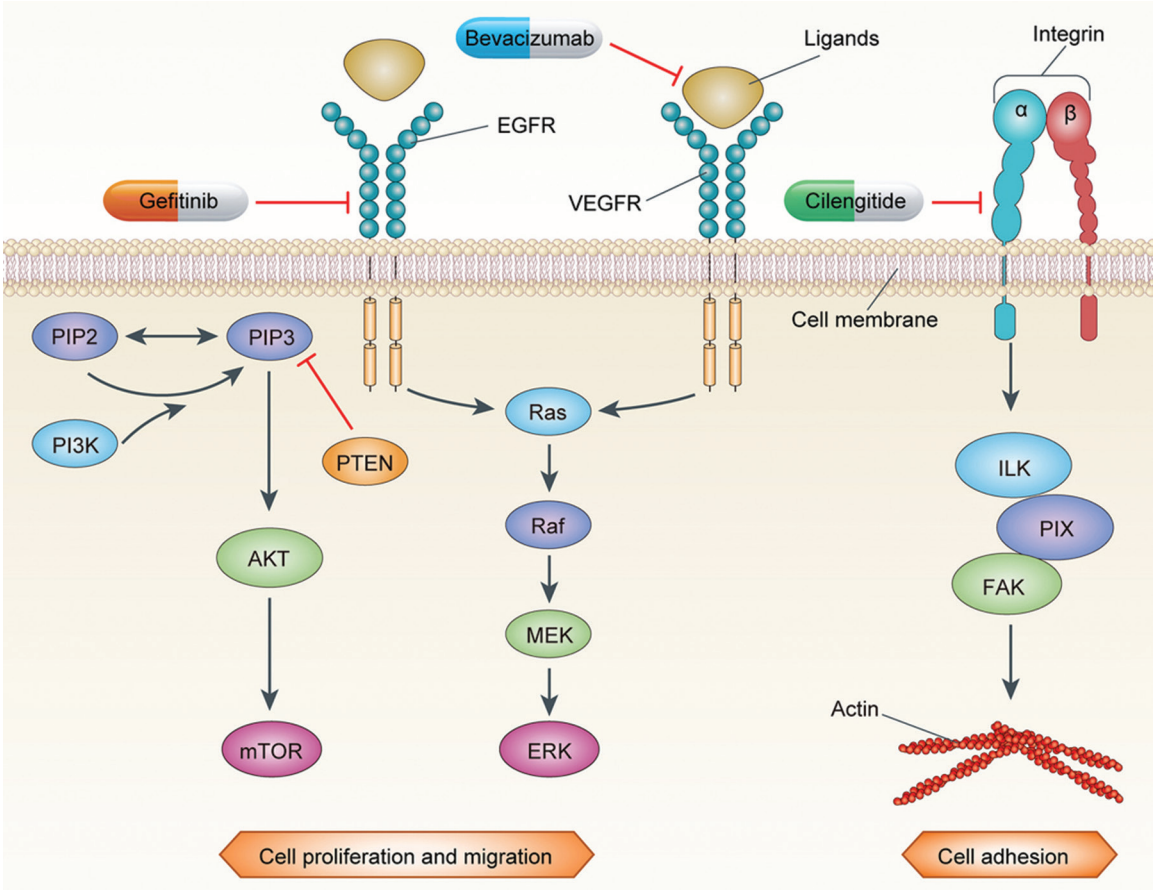

Figure 1. Pathogenesis of involves many signaling, such as PI3K-AKT, EGFR, VEGFR and integrin signaling pathway, which regulates tumor cells proliferation, migration and adhesion. Several drugs have been developed to treat gliomas by targeting different pathway.

by receptor tyrosine kinases, PI3K phosphorylates PIP2 to generate PIP3 and activates the signaling pathway. V-akt murine thymoma viral oncogene homolog (AKT) is activated downstream of PIP3 and mediates such physiological processes as cell proliferation, migration and metabolism (Figure 1). The PI3K/PTEN/AKT pathway is critical for angiogenesis, cell proliferation and survival (65). Of note, the over-activation or constitutive activation of PI3K as well as the loss of PTEN function results in the accumulation of cellular PIP3 and its activated downstream pathway. Particularly, the loss of function in the mutations of PTEN is frequently found in GBM (66, 67). Epigenetic gene silencing by promoter methylation also inactivates PTEN. In animal models, haploinsufficiency is sufficient to promote tumorigenesis for certain tumor types, and progressive reduction of PTEN results in increasingly aggressive tumors (68). Transfection of PTEN leads to reduced proliferation and induction of cell cycle arrest at G0/G1, accompanied by inactivation of AKT phosphorylation at Ser-473 (69). In addition, exogenous PTEN expression induces astrocytic differentiation in the presence of the extracellular matrix (ECM), while neural stem cells self-renewal is negatively regulated by modulating G0-G1 cell cycle entry. PTEN expression sensitizes GBM cells to radiation, but not to chemotherapeutic drugs. Consistently, epigenetic and genetic inactivation of PTEN is associated with shorter survival in GBM patients (66, 67).

5.3. RB protein pathway

The RB tumor suppressor is well known for its ability to repress transcription and to prevent cell proliferation by arresting cells either in G1, at the G1/S transition, or in S phase of the cell cycle. Through its effects on E2F, the loss of RB alters the expression of numerous proteins that are needed for S-phase. RB/E2F proteins have also been shown to physically interact with replication factors RB. The functional inactivation of RB compromises the ability of cells to respond to signals that normally suppress cell proliferation and result in the overexpression of genes that drive cell division. The Rb1 gene is located on chromosome 13q14, which is mutated in 25% of high-grade gliomas. The loss of 13q is characteristic of transition from low-grade to intermediate-grade gliomas (70-72).

5.4. EGFR signaling pathway

EGFR is a transmembrane glycoprotein that constitutes one of four members of the ErbB family of tyrosine kinase receptors. EGFR is activated by binding of a ligand to the extracellular domain, leading to receptor dimerization and subsequent activation of tyrosine kinases in the intracellular domain. The tyrosine kinase, in turn, activates a complex downstream signaling network (73). Downstream signaling pathways, like PI3K-AKT, PI3K-Rac-Rho, Ras-Raf-Mek-Erk and Jak-STAT, play multiple roles in cell proliferation, migration, invasion, resistance to apoptosis, and tumor neovascularization (Figure 1). Genetic alterations like overexpression, small deletions or mutations can lead to oncogenic upregulation of EFGR. Overexpression of EGFR has been found in many different tumor types, including GBM, and has been consistently found to be correlated with a poor outcome (74). In GBM, activation of EGFR is present in 40–60% of tumors (75). Amplification of the EGFR gene is often associated with a mutation that encodes for a truncated form of the receptor, known as EGFRvIII, lacking the extracellular binding domain and leading to constitutive activation of tyrosine kinases. EFGRvIII is the most frequent EGFR mutation in GBM (76). Expression of EGFRvIII correlates with poor survival in GBM patients and promotes glioma cell migration, tumor growth, invasion, survival and angiogenesis. Furhtermore, EGFRvIII causes enhanced apoptosis resistance. Activated EGFR is also related to radio- and chemo-resistance in GBM cells (77).

5.5. Platelet-derived growth factor (PDGF) signaling pathway

PDGF consists of four isoforms: PDGF-A, PDGF-B, PDGF-C and PDGF-D. Once bound by ligand, receptor dimerization leads to autophosphorylation on tyrosine residues, which then activates the PI3k and Src pathways. The PDGF pathway is implicated in angiogenesis, wound healing and cancer cell growth via autocrine/paracrine stimulatory loops (78). PDGFRα and its ligands, PDGF-A and PDGF-B, are represented in gliomas, especially in high-grade gliomas. Increased expression of PDGFRβ has been reported in proliferating endothelial cells of GBM. PDGF-C and PDGF-D, which require proteolytic cleavage to be activated, are also frequently expressed in glioma cell lines and in GBM-derived tissues (79, 80).

5.6. IDH

IDH is an enzyme that catalyzes the oxidative decarboxylation of isocitrate, producing α-ketoglutarate and CO_2. This is a two-step process, which involves oxidation of isocitrate to oxalosuccinate, followed by the decarboxylation of the carboxyl group beta to a ketone, forming α-ketoglutarate (81). Mutations in gliomas frequently occur in either isocitrate IDH 1 or 2 genes. One of these mutations (mostly in IDH1) occurs in about 80% of low-grade gliomas and secondary high-grade gliomas. IDH1 and IDH2 mutant cells produce an excess metabolic intermediate, 2-hydroxyglutarate, which binds to catalytic sites in key enzymes that are important in altering histone and DNA promoter methylation (82, 83). Thus, mutations in IDH1 and IDH2 generate a “DNA CpG island methylator phenotype or CIMP” that causes promoter hypermethylation and concomitant silencing of tumor suppressor genes, such as DNA repair genes MGMT and ERCC1(84). Additionally,, mutations in IDH1 or IDH2 can cause increased oxidative stress. Increased oxidative damage to DNA may be mutagenic. As a result,, IDH1 or IDH2 mutations act as driver mutations in glioma carcinogenesis, though the primary mechanism is unclear (84).

6. POTENTIAL TARGETS OF GLIOMAS MANAGEMENT

Maximal safe surgical resection remains the initial standard of care for glioma patients, especially for GBM. Surgical resection provides histological diagnosis, symptomatic relief and a reduction in tumor burden. However, due to the infiltrative nature of GBM and frequent proximity to critical neural structures, complete resection is often not feasible. Radiotherapy with concurrent and adjuvant temozolomide (TMZ) has become the standard of care following maximal safe resection in patients with newly diagnosed GBM (85, 86). Despite the survival benefit established with combination radiotherapy and TMZ, outcomes in GBM remain poor. Molecular targeting tailored to tumor biology has now taken hold in the field of oncology, and similar approaches are being developed for GBM.

6.1. EGFR inhibitors

Mutation and altered expression of EGFR were related with glioma development; therefore, several EGFR inhibitors have been applied into treatment against glioma. Erlotinib, an oral EGFR tyrosine kinase inhibitor, has recently been evaluated in GBM. A single arm phase II trial enrolled 65 patients with newly diagnosed GBM to concurrent radiotherapy with TMZ plus erlotinib followed by TMZ and erlotinib. Overall survival (OS) in this study was significantly improved when compared with historical controls (19.3. vs 14.1. months; p = 0.0.1).

Gefitinib is another oral EGFR tyrosine kinase inhibitor (Figure 1). A single arm phase II trial enrolled patients with newly diagnosed GBM to receive gefitinib following surgical resection and radiotherapy. The study again did not show a benefit in OS or progression-free survival (PFS). However, subgroup analysis of patients who experienced gefitinib-related diarrhea did have statistically significant improvements in OS and PFS. Of note, both studies with gefitinib were conducted prior to the known benefit of concurrent TMZ with radiotherapy, which makes it difficult to draw firm conclusions on the potential use of gefitinib in the setting of TMZ use (87, 88).

The EGFRvIII mutant receptor, the most commonly identified EGFR mutant, is generated from

an in-frame deletion of exons 2–7 of the EGFR gene, which leads to constitutively active signaling in the absence of ligand binding. Rindopepimut is a synthetic peptide designed from EGFR-vIII and cysteine residues, which can be administered as a vaccine intradermally and produces an EGFRvIII-specific immune response (89, 90). A Phase II trial enrolled patients with EGFRvIII mutant containing GBM to receive rindopepimut following surgery and concurrent radiotherapy with TMZ. The median OS was 26 months and PFS was 14.2. months, an improvement over case-matched controls of patients traditionally treated with radiotherapy and TMZ (89, 90). The median OS for the six patients who developed an EGFRvIII-specific antibody response was 47.7. months, and for the eight patients who did not, the median OS was much shorter at 22.8. months. Based on the promising results from this phase II study, a phase III study is now in progress, testing rindopepimut in patients with newly diagnosed GBM (89, 90).

6.2. Vascular endothelial growth factor (VEGF) inhibitors

VEGF is a key regulator of angiogenesis, which consists of five proteins: VEGF-A, VEGF-B, VEGF-C, VEGF-D and PlGF (91). VEGF-A is responsible for the rate-limiting step in normal and tumor blood vessel growth, while VEGF-C and VEGF-D regulate lymphatic angiogenesis. There are two VEGF receptor tyrosine kinases, VEGFR-1 and VEGFR-2. VEGFR-1 is believed to sequester VEGF and prevent interaction; while VEGFR-2 is the principal mediator of the VEGF response. Once bound by ligand, VEGFR-2 leads to dimerization, tyrosine residue phosphorylation, and ultimately regulation of angiogenesis, cell proliferation, and survival. Since VEGF expression in GBM is usually highest adjacent to necrotic regions among the population of hypoxic tumor cells, VEGF inhibitors represent particularly effective therapy in GBM (91). Bevacizumab (Avastin) is a humanized monoclonal antiangiogenic antibody specific against VEGF-A, which has been found to be a promising agent alone or in combination with chemotherapy in a variety of solid tumors (92-94) (Figure 1). Historically, the 6-month PFS is poor in patients with recurrent disease at 15.7.% when treated with irinotecan alone. The addition of bevacizumab to irinotecan was tested in 35 patients in a single arm phase II study, and the 6-month PFS was improved to 46%. This study led to a randomized phase II study in recurrent GBM, allocating patients to bevacizumab alone versus bevacizumab plus irinotecan. Bevacizumab alone was significantly better than historical controls with a 6-month PFS of 42.6.% ($p < 0.0.001$). Combination therapy with bevacizumab plus irinotecan proved even more efficacious with a 6-month PFS of 50.3.% (92-94).

6.3. Integrin inhibitors

To migrate and invade, a glioma cell must establish transient adhesive interactions with the ECM where a biphasic relationship between strength of adhesion and migration speed has been proposed. The most important group of adhesion molecules is the transmembrane proteins, integrins, that form dimers between 14 different α and 8 β subunits. Integrins bind ligands, including fibronectin, laminin, vitronectin, thrombospondin, fibrinogen/fibrin, matrix metalloproteinase -2 and fibroblast growth factor 2, at specific arginine-glycine-aspartic acid (RGD) sequences. Once bound by ligand, integrins activate signaling cascades that mediate cellular adhesion, proliferation, survival and migration. Integrins also play a role in angiogenesis, where they are critical for endothelial cell proliferation, survival and migration. Of note, the vascular integrins, αVβ3and αVβ5, are being targeted in clinical trials as antineoplastic agents (95). Cilengitide is an inhibitor of αVβ3and αVβ5 integrins (Figure 1). In a phase I/II study, newly diagnosed GBM patients were treated with cilengitide at a dose of 500 mg twice weekly plus TMZ with concurrent radiotherapy (96). Cilengitide was given one week prior to chemoradiotherapy and continued until the end of adjuvant TMZ or progression of disease. The primary end point of six month PFS was 69%, an improvement over RT with TMZ alone by approximately 15% (96).

7. PERSPECTIVE

Emerging techniques such as gene profiling by microarray and proteome analysis have provided powerful approaches to identifying new critical genes and aided in defining molecular classification based on homogenous clusters of tumors. This review has discussed various candidate genes that were mutated or altered in expression during occurrence and development of glioma. The next step aims to be the identification of the molecules which play a role in glioma pathogenesis and are promising as therapeutic targets on the candidate gene list. Despite the strong rationale of clinical trials with genetic targets, most studies have shown very modest results. The negative results reported in the majority of published clinical studies may be explained, at least in part, by single-targeted approaches, which may be limited by factors such as tumor heterogenity and genetic instability. Thus, new trends on glioma-targeted therapies should not focus on a single genetic pathway, but should try to interact in different molecular pathways.

8. ACKNOWLEDGEMENTS

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9. REFERENCE

1. P. de Robles, K. M. Fiest, A. D. Frolkis, T. Pringsheim, C. Atta, C. St Germaine-Smith:

The worldwide incidence and prevalence of primary brain tumors: a systematic review and meta-analysis. *Neuro Oncol* (2014)
DOI: 10.1093/neuonc/nou283

2. Q. T. Ostrom, H. Gittleman, P. Liao, C. Rouse, Y. Chen, J. Dowling, Y. Wolinsky, C. Kruchko and J. Barnholtz-Sloan: CBTRUS Statistical Report: Primary Brain and Central Nervous System Tumors Diagnosed in the United States in 2007-2011. *Neuro Oncol* (2014)
DOI: 10.1093/neuonc/nou223
3. S. Takahashi: (2. Diseases of the brain 2: brain tumors). *Nihon Hoshasen Gijutsu Gakkai Zasshi* 70(9), 1095-105 (2014)
DOI: 10.6009/jjrt.2014_JSRT_70.9.1095
4. B. Shofty, S. Constantini, F. Bokstein, Z. Ram, L. Ben-Sira, S. Freedman, G. Vainer: Optic pathway gliomas in adults. *Neurosurgery* 74(3), 273-9 (2013)
DOI: 10.1227/NEU.0000000000000257
5. T. Schneider, C. Mawrin, C. Scherlach, M. Skalej and R. Firsching: Gliomas in adults. *Dtsch Arztebl Int* 107(45), 799-807 (2010)
Doi not found
6. P. Y. Wen and S. Kesari: Malignant gliomas in adults. *N Engl J Med* 359(5), 492-507 (2008)
DOI: 10.1056/NEJMra0708126
7. M. L. Goodenberger and R. B. Jenkins: Genetics of adult glioma. *Cancer Genet* 205(12), 613-21 (2012)
DOI: 10.1016/j.cancergen.2012.10.009
8. J. P. Posti, M. Bori, T. Kauko, M. Sankinen, J. Nordberg, M. Rahi, J. Frantzen, V. Vuorinen: Presenting symptoms of glioma in adults. *Acta Neurol Scand* (2014)
DOI: 10.1111/ane.12285
9. E. M. Sizoo, L. Braam, T. J. Postma, H. R. Pasman, J. J. Heimans, M. Klein: Symptoms and problems in the end-of-life phase of high-grade glioma patients. *Neuro Oncol* 12(11), 1162-6 (2010)
DOI: 10.1093/neuonc/nop045
10. N. Yamaguchi: (The IARC carcinogenicity evaluation of radio-frequency electromagnetic field: with special reference to epidemiology of mobile phone use and brain tumor risk). *Nihon Eiseigaku Zasshi* 68(2), 78-82 (2013)
DOI: 10.1265/jjh.68.78
11. V. S. Benson, K. Pirie, J. Schuz, G. K. Reeves, V. Beral and J. Green: Mobile phone use and risk of brain neoplasms and other cancers: prospective study. *Int J Epidemiol* 42(3), 792-802 (2010)
DOI: 10.1093/ije/dyt072
12. C. O. Da Fonseca, J. T. Silva, I. R. Lins, M. Simao, A. Arnobio, D. Futuro: Correlation of tumor topography and peritumoral edema of recurrent malignant gliomas with therapeutic response to intranasal administration of perillyl alcohol. *Invest New Drugs* 27(6), 557-64 (2009)
DOI: 10.1007/s10637-008-9215-3
13. K. M. Kurian, H. R. Haynes, C. Crosby, K. Hopkins and M. Williams: IDH mutation analysis in gliomas as a diagnostic and prognostic biomarker. *Br J Neurosurg* 27(4), 442-5 (2013)
DOI: 10.3109/02688697.2013.771139
14. K. Ichimura: Molecular pathogenesis of IDH mutations in gliomas. *Brain Tumor Pathol* 29(3), 131-9 (2012)
DOI: 10.1007/s10014-012-0090-4
15. G. Lombardi, A. Della Puppa, A. L. Di Stefano, A. Pace, R. Ruda, E. Tabouret and V. Zagonel: Gliomas. *Biomed Res Int* (2014)
Doi not found
16. S. Trabelsi, D. H. Brahim, M. Ladib, N. Mama, I. Harrabi, K. Tlili: Glioma epidemiology in the central tunisian population: 1993-2012. *Asian Pac J Cancer Prev* 15(20), 8753-7 (2014)
Doi not found
17. Q. T. Ostrom, L. Bauchet, F. G. Davis, I. Deltour, J. L. Fisher, C. E. Langer: The epidemiology of glioma in adults: a “state of the science” review. *Neuro Oncol* 16(7), 896-913 (2014)
DOI: 10.1093/neuonc/nou087
18. J. Rineer, D. Schreiber, K. Choi and M. Rotman: Characterization and outcomes of infratentorial malignant glioma: a population-based study using the Surveillance Epidemiology and End-Results database. *Radiother Oncol* 95(3), 321-6 (2010)
DOI: 10.1016/j.radonc.2010.04.007
19. W. Wick and M. Weller: Classification and management of anaplastic gliomas. *Curr Opin Neurol* 22(6), 650-6 (2009)
DOI: 10.1097/WCO.0b013e3283329ce7
20. D. Figarella-Branger, C. Colin, B. Coulibaly, B. Quilichini, A. Maues De Paula, C. Fernandez: (Histological and molecular classification of

gliomas). *Rev Neurol (Paris)* 164(6-7), 505-15 (2008)
DOI: 10.1016/j.neurol.2008.03.011

21. A. Araque and M. Navarrete: Glial cells in neuronal network function. *Philos Trans R Soc Lond B Biol Sci*,365(1551), 2375-81 (2009)
DOI: 10.1098/rstb.2009.0313

22. E. Lopez-Bayghen and A. Ortega: (Glial cells and synaptic activity: translational control of metabolic coupling). *Rev Neurol* 50(10), 607-15 (2010)
Doi not found

23. Y. Li, X. F. Du and J. L. Du: (Physiological properties and functions of microglia). *Sheng Li Xue Bao* 65(5), 471-82 (2013)
Doi not found

24. H. Wake, A. J. Moorhouse and J. Nabekura: Functions of microglia in the central nervous system--beyond the immune response. *Neuron Glia Biol* 7(1), 47-53 (2012)
DOI: 10.1017/S1740925X12000063

25. A. S. Harms, J. K. Lee, T. A. Nguyen, J. Chang, K. M. Ruhn, I. Trevino: Regulation of microglia effector functions by tumor necrosis factor signaling. *Glia* 60(2), 189-202 (2011)
DOI: 10.1002/glia.21254

26. L. B. Buckman and K. L. Ellacott: The contribution of hypothalamic macroglia to the regulation of energy homeostasis. *Front Syst Neurosci* 8, 212 (2014)
DOI: 10.3389/fnsys.2014.00212

27. A. Hafidi and D. Galifianakis: Macroglia distribution in the developing and adult inferior colliculus. *Brain Res Dev Brain Res* 143(2), 167-77 (2003)
DOI: 10.1016/S0165-3806(03)00110-X

28. M. J. Ramirez-Exposito and J. M. Martinez-Martos: (Structure and functions of the macroglia in the central nervous system. Response to degenerative disorders). *Rev Neurol* 26(152), 600-11 (1998)
Doi not found

29. F. Lefranc, M. Rynkowski, O. DeWitte and R. Kiss: Present and potential future adjuvant issues in high-grade astrocytic glioma treatment. *Adv Tech Stand Neurosurg* 34, 3-35 (2009)
DOI: 10.1007/978-3-211-78741-0_1

30. F. B. Furnari, T. Fenton, R. M. Bachoo, A. Mukasa, J. M. Stommel, A. Stegh, W. C. Hahn, K. L. Ligon, D. N. Louis: Malignant astrocytic glioma: genetics, biology, and paths to treatment. *Genes Dev* 21(21), 2683-710 (2007)
DOI: 10.1101/gad.1596707

31. A. Pusateri and C. E. Margo: Intraocular astrocytoma and its differential diagnosis. *Arch Pathol Lab Med* 138(9), 1250-4 (2013)
DOI: 10.5858/arpa.2013-0448-RS

32. V. Suri, P. Jha, S. Agarwal, P. Pathak, M. C. Sharma, V. Sharma: Molecular profile of oligodendrogliomas in young patients. *Neuro Oncol* 13(10), 1099-106 (2011)
DOI: 10.1093/neuonc/nor146

33. F. Zustovich, A. Della Puppa, R. Scienza, P. Anselmi, C. Furlan and G. Cartei: Metastatic oligodendrogliomas: a review of the literature and case report. *Acta Neurochir (Wien)* 150(7), 699-702; discussion 702-3 (2008)
DOI: 10.1007/s00701-008-1507-z

34. J. E. Bromberg and M. J. van den Bent: Oligodendrogliomas: molecular biology and treatment. *Oncologist* 14(2), 155-63 (2009)
DOI: 10.1634/theoncologist.2008-0248

35. P. C. McCormick: Ependymomas. *J Neurosurg Spine* 19(1), 1-2 (2013)
DOI: 10.3171/2013.1.SPINE121111

36. S. J. Baloyannis and I. S. Baloyannis: The fine structure of ependymomas. *CNS Oncol* 3(1), 49-59 (2014)
DOI: 10.2217/cns.13.64

37. C. Bettegowda, O. Adogwa, V. Mehta, K. L. Chaichana, J. Weingart, B. S. Carson: Treatment of choroid plexus tumors: a 20-year single institutional experience. *J Neurosurg Pediatr* 10(5), 398-405 (2012)
DOI: 10.3171/2012.8.PEDS12132

38. A. E. Gozali, B. Britt, L. Shane, I. Gonzalez, F. Gilles, J. G. McComb, M. D. Krieger: Choroid plexus tumors; management, outcome, and association with the Li-Fraumeni syndrome: the Children's Hospital Los Angeles (CHLA) experience, 1991-2010. *Pediatr Blood Cancer* 58(6), 905-9 (2011)
DOI: 10.1002/pbc.23349

39. D. R. Laks, K. Visnyei and H. I. Kornblum: Brain tumor stem cells as therapeutic targets in models of glioma. *Yonsei Med J* 51(5), 633-40 (2010)
DOI: 10.3349/ymj.2010.51.5.633

40. A. Rousseau, K. Mokhtari and C. Duyckaerts: The 2007 WHO classification of tumors of the central nervous system - what has changed? *Curr Opin Neurol* 21(6), 720-7 (2008) DOI: 10.1097/WCO.0b013e328312c3a7

41. Q. Zhou: [WHO classification of tumors of central nervous system (2007): an introduction). *Zhonghua Bing Li Xue Za Zhi* 37(1), 5-7] (2008)

42. D. N. Louis, H. Ohgaki, O. D. Wiestler, W. K. Cavenee, P. C. Burger, A. Jouvet: The 2007 WHO classification of tumours of the central nervous system. *Acta Neuropathol* 114(2), 97-109 (2007) DOI: 10.1007/s00401-007-0243-4

43. S. K. Carlsson, S. P. Brothers and C. Wahlestedt: Emerging treatment strategies for glioblastoma multiforme. *EMBO Mol Med* 6(11), 1359-1370 (2013) DOI: 10.15252/emmm.201302627

44. H. Cholewa, K. Duda, K. Labuzek and B. Okopien: (The newest perspectives on the treatment of glioblastoma multiforme). *Pol Merkur Lekarski* 37(218), 119-23 (2014) Doi not found

45. Y. Zhang, Y. Pan and X. Li: Glioblastoma multiforme in the brainstem in a young adult. *Clin Neurol Neurosurg*, 124, 175-8 (2014) DOI: 10.1016/j.clineuro.2014.06.039

46. T. Scarabino, G. M. Giannatempo, F. Nemore, T. Popolizio and A. Stranieri: Supratentorial low-grade gliomas. Neuroradiology. *J Neurosurg Sci*, 49(3), 73-6 (2005) Doi not found

47. T. Miwa, Y. Hirose, H. Sasaki, E. Ikeda, K. Yoshida and T. Kawase: Genetic characterization of adult infratentorial gliomas. *J Neurooncol*, 91(3), 251-5 (2009) DOI: 10.1007/s11060-008-9714-2

48. M. H. Handler and N. K. Foreman: Pontine gliomas. *J Neurosurg Pediatr* 5(1), 140-1 (2009) DOI: 10.3171/2009.5.PEDS09265

49. I. Pascual-Castroviejo, A. Martinez Bermejo, V. Lopez Martin, C. Roche and S. I. Pascual Pascual: Optic gliomas in neurofibromatosis type 1 (NF-1). Presentation of 31 cases. *Neurologia* 9(5), 173-7 (1994) Doi not found

50. E. Hewer, L. Mariani and I. Vajtai: Glioma-like proliferation in a cortical hamartoma of tuberous sclerosis complex. *Brain Tumor Pathol* (2014) DOI: 10.1007/s10014-014-0185-1

51. I. Fischer, C. Cunliffe, R. J. Bollo, H. L. Weiner, O. Devinsky, M. E. Ruiz-Tachiquin, T. Venuto, A. Pearlman, L. Chiriboga, R. J. Schneider, H. Ostrer and D. C. Miller: Glioma-like proliferation within tissues excised as tubers in patients with tuberous sclerosis complex. *Acta Neuropathol* 116(1), 67-77 (2008) DOI: 10.1007/s00401-008-0391-1

52. E. J. Uhlmann and S. R. Plotkin: Neurofibromatoses. *Adv Exp Med Biol* 724, 266-77 (2012) DOI: 10.1007/978-1-4614-0653-2_20

53. M. J. Rabito and A. D. Kaye: Tuberous sclerosis complex: perioperative considerations. *Ochsner J* 14(2), 229-39 (2014) Doi not found

54. P. Virag, I. Brie, E. Fischer-Fodor, M. Perde-Schrepler, C. Tatomir, O. Balacescu: Assessment of cytotoxicity, apoptosis and DNA damages in Colo320 colorectal cancer cells selected for oxaliplatin resistance. *Cell Biochem Funct* 29(5), 351-5 (2011) DOI: 10.1002/cbf.1754

55. K. Iwai, S. Adachi, M. Takahashi, L. Moller, T. Udagawa, S. Mizuno and I. Sugawara: Early oxidative DNA damages and late development of lung cancer in diesel exhaust-exposed rats. *Environ Res* 84(3), 255-64 (2000) DOI: 10.1006/enrs.2000.4072

56. G. Yuan, D. Gao, S. Ding and J. Tan: DNA repair gene ERCC1 polymorphisms may contribute to the risk of glioma. *Tumour Biol* 35(5), 4267-75 (2014) DOI: 10.1007/s13277-013-1557-6

57. P. Rajaraman, A. Hutchinson, S. Wichner, P. M. Black, H. A. Fine, J. S. Loeffler: DNA repair gene polymorphisms and risk of adult meningioma, glioma, and acoustic neuroma. *Neuro Oncol* 12(1), 37-48 (2010) DOI: 10.1093/neuonc/nop012

58. V. Milinkovic, J. Bankovic, M. Rakic, N. Milosevic, T. Stankovic, M. Jokovic: Genomic instability and p53 alterations in patients with malignant glioma. *Exp Mol Pathol* 93(2), 200-6 (2012) DOI: 10.1016/j.yexmp.2012.05.010

59. C. D. James: p53 in malignant glioma: 20 years later and still much to learn. *Neuro Oncol*, 12(5), 421 (2010)
Doi not found

60. M. K. Sibin, D. I. Bhat, C. Lavanya, M. J. Manoj, S. Aakershita and G. K. Chetan: CDKN2A exon-wise deletion status and novel somatic mutations in Indian glioma patients. *Tumour Biol* 35(2), 1467-72 (2013)
DOI: 10.1007/s13277-013-1201-5

61. C. Hartmann, L. Kluwe, M. Lucke and M. Westphal: The rate of homozygous CDKN2A/p16 deletions in glioma cell lines and in primary tumors. *Int J Oncol* 15(5), 975-82 (1999)
Doi not found

62. N. Ishii, D. Maier, A. Merlo, M. Tada, Y. Sawamura, A. C. Diserens: Frequent co-alterations of TP53, p16/CDKN2A, p14ARF, PTEN tumor suppressor genes in human glioma cell lines. *Brain Pathol* 9(3), 469-79 (1999)
DOI: 10.1111/j.1750-3639.1999.tb00536.x

63. N. Senzer, J. Nemunaitis, M. Nemunaitis, J. Lamont, M. Gore, H. Gabra: p53 therapy in a patient with Li-Fraumeni syndrome. *Mol Cancer Ther* 6(5), 1478-82 (2007)
DOI: 10.1158/1535-7163.MCT-07-0125

64. L. S. Steelman, W. H. Chappell, S. L. Abrams, R. C. Kempf, J. Long, P. Laidler: Roles of the Raf/MEK/ERK and PI3K/PTEN/Akt/mTOR pathways in controlling growth and sensitivity to therapy-implications for cancer and aging. *Aging (Albany NY)* 3(3), 192-222 (2011)
Doi not found

65. H. J. Lim, P. Crowe and J. L. Yang: Current clinical regulation of PI3K/PTEN/Akt/mTOR signalling in treatment of human cancer. *J Cancer Res Clin Oncol* (2014)
DOI: 10.1007/s00432-014-1803-3

66. G. A. Alexiou and S. Voulgaris: The role of the PTEN gene in malignant gliomas. *Neurol Neurochir Pol* 44(1), 80-6 (2010)
DOI: 10.1016/S0028-3843(14)60408-4

67. C. B. Knobbe, A. Merlo and G. Reifenberger: Pten signaling in gliomas. *Neuro Oncol* 4(3), 196-211 (2002)
DOI: 10.1215/15228517-4-3-196

68. J. K. Wiencke, S. Zheng, N. Jelluma, T. Tihan, S. Vandenberg, T. Tamguney: Methylation of the PTEN promoter defines low-grade gliomas and secondary glioblastoma. *Neuro Oncol* 9(3), 271-9 (2007)
DOI: 10.1215/15228517-2007-003

69. Y. Yang, N. Shao, G. Luo, L. Li, L. Zheng, P. Nilsson-Ehle and N. Xu: Mutations of PTEN gene in gliomas correlate to tumor differentiation and short-term survival rate. *Anticancer Res* 30(3), 981-5 (2010)
Doi not found

70. D. A. Hilton, M. Penney, B. Evans, H. Sanders and S. Love: Evaluation of molecular markers in low-grade diffuse astrocytomas: loss of p16 and retinoblastoma protein expression is associated with short survival. *Am J Surg Pathol* 26(4), 472-8 (2002)
DOI: 10.1097/00000478-200204000-00009

71. J. W. Henson, B. L. Schnitker, K. M. Correa, A. von Deimling, F. Fassbender, H. J. Xu: The retinoblastoma gene is involved in malignant progression of astrocytomas. *Ann Neurol* 36(5), 714-21 (1994)
DOI: 10.1002/ana.410360505

72. J. N. Rich, C. Guo, R. E. McLendon, D. D. Bigner, X. F. Wang and C. M. Counter: A genetically tractable model of human glioma formation. *Cancer Res* 61(9), 3556-60 (2001)
Doi not found

73. Y. Yarden: The EGFR family and its ligands in human cancer. signalling mechanisms and therapeutic opportunities. *Eur J Cancer* 37 Suppl 4, S3-8 (2001)
DOI: 10.1016/S0959-8049(01)00230-1

74. T. A. Libermann, H. R. Nusbaum, N. Razon, R. Kris, I. Lax, H. Soreq: Amplification and overexpression of the EGF receptor gene in primary human glioblastomas. *J Cell Sci Suppl* 3, 161-72 (1985)
DOI: 10.1242/jcs.1985.Supplement_3.16

75. J. L. Nakamura: The epidermal growth factor receptor in malignant gliomas: pathogenesis and therapeutic implications. *Expert Opin Ther Targets* 11(4), 463-72 (2007)
DOI: 10.1517/14728222.11.4.463

76. M. T. Stockhausen, H. Broholm, M. Villingshoj, M. Kirchhoff, T. Gerdes, K. Kristoffersen: Maintenance of EGFR and EGFRvIII expressions in an *in vivo* and *in vitro* model of human glioblastoma multiforme. *Exp Cell Res*

317(11), 1513-26 (2011)
DOI: 10.1016/j.yexcr.2011.04.001

77. R. Altieri, A. Agnoletti, F. Quattrucci, D. Garbossa, F. M. Calamo Specchia, M. Bozzaro: Molecular biology of gliomas: present and future challenges. *Transl Med UniSa* 10, 29-37 (2014)
Doi not found

78. J. Paulsson, M. Ehnman and A. Ostman: PDGF receptors in tumor biology: prognostic and predictive potential. *Future Oncol* 10(9), 1695-708 (2014)
DOI: 10.2217/fon.14.83

79. N. Lindberg and E. C. Holland: PDGF in gliomas: more than just a growth factor? *Ups J Med Sci* 117(2), 92-8 (2012)
DOI: 10.3109/03009734.2012.654860

80. A. Mauro, A. Bulfone, E. Turco and D. Schiffer: Coexpression of platelet-derived growth factor (PDGF) B chain and PDGF B-type receptor in human gliomas. *Childs Nerv Syst* 7(8), 432-6 (1991)
DOI: 10.1007/BF00263184

81. K. E. Yen and D. P. Schenkein: Cancer-associated isocitrate dehydrogenase mutations. *Oncologist*, 17(1), 5-8 (2012)
DOI: 10.1634/theoncologist.2011-0429

82. M. Megova, J. Drabek, V. Koudelakova, R. Trojanec, O. Kalita and M. Hajduch: Isocitrate dehydrogenase 1 and 2 mutations in gliomas. *J Neurosci Res* 92(12), 1611-20 (2014)
DOI: 10.1002/jnr.23456

83. L. Yu, S. T. Qi and Z. Y. Li: Analysis of isocitrate dehydrogenase-1/2 gene mutations in gliomas. *Chin Med J (Engl)* 123(24), 3697-705 (2011)
Doi not found

84. C. Guo, C. J. Pirozzi, G. Y. Lopez and H. Yan: Isocitrate dehydrogenase mutations in gliomas: mechanisms, biomarkers and therapeutic target. *Curr Opin Neurol* 24(6), 648-52 (2011)
DOI: 10.1097/WCO.0b013e32834cd415

85. G. Minniti, V. De Sanctis, R. Muni, F. Filippone, A. Bozzao, M. Valeriani: Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma in elderly patients. *J Neurooncol* 88(1), 97-103 (2008)
DOI: 10.1007/s11060-008-9538-0

86. R. Stupp, W. P. Mason, M. J. van den Bent, M. Weller, B. Fisher, M. J. Taphoorn: Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med* 352(10), 987-96 (2005)
DOI: 10.1056/NEJMoa043330

87. M. D. Prados, S. M. Chang, N. Butowski, R. DeBoer, R. Parvataneni, H. Carliner: Phase II study of erlotinib plus temozolomide during and after radiation therapy in patients with newly diagnosed glioblastoma multiforme or gliosarcoma. *J Clin Oncol* 27(4), 579-84 (2009)
DOI: 10.1200/JCO.2008.18.9639

88. M. J. van den Bent, A. A. Brandes, R. Rampling, M. C. Kouwenhoven, J. M. Kros, A. F. Carpentier: Randomized phase II trial of erlotinib versus temozolomide or carmustine in recurrent glioblastoma: EORTC brain tumor group study 26034. *J Clin Oncol* 27(8), 1268-74 (2009)
DOI: 10.1200/JCO.2008.17.5984

89. J. H. Sampson, G. E. Archer, D. A. Mitchell, A. B. Heimberger, J. E. Herndon,: An epidermal growth factor receptor variant III-targeted vaccine is safe and immunogenic in patients with glioblastoma multiforme. *Mol Cancer Ther* 8(10), 2773-9 (2009)
DOI: 10.1158/1535-7163.MCT-09-0124

90. J. H. Sampson, A. B. Heimberger, G. E. Archer, K. D. Aldape, A. H. Friedman, H. S. Friedman: Immunologic escape after prolonged progression-free survival with epidermal growth factor receptor variant III peptide vaccination in patients with newly diagnosed glioblastoma. *J Clin Oncol* 28(31), 4722-9 (2010)
DOI: 10.1200/JCO.2010.28.6963

91. D. Sia, C. Alsinet, P. Newell and A. Villanueva: VEGF signaling in cancer treatment. *Curr Pharm Des* 20(17), 2834-42 (2013)
DOI: 10.2174/13816128113199990590

92. L. W. Buie and J. Valgus: Bevacizumab: a treatment option for recurrent glioblastoma multiforme. *Ann Pharmacother* 42(10), 1486-90 (2008)
DOI: 10.1345/aph.1L030

93. J. J. Vredenburgh, A. Desjardins, J. E. Herndon, 2nd, J. Marcello, D. A. Reardon, J. A. Quinn: Bevacizumab plus irinotecan in recurrent glioblastoma multiforme. *J Clin Oncol* 25(30), 4722-9 (2007)
DOI: 10.1200/JCO.2007.12.2440

94. D. A. Reardon, A. Desjardins, J. J. Vredenburgh, S. Gururangan, J. H. Sampson, S. Sathornsumetee, R. E. McLendon: Metronomic chemotherapy with daily, oral etoposide plus bevacizumab for recurrent malignant glioma: a phase II study. *Br J Cancer* 101(12), 1986-94 (2009) DOI: 10.1038/sj.bjc.6605412

95. N. Kannan, L. V. Nguyen and C. J. Eaves: Integrin beta3 links therapy resistance and cancer stem cell properties. *Nat Cell Biol* 16(5), 397-9 (2014) DOI: 10.1038/ncb2960

96. R. Stupp, M. E. Hegi, B. Neyns, R. Goldbrunner, U. Schlegel, P. M. Clement: Phase I/IIa study of cilengitide and temozolomide with concomitant radiotherapy followed by cilengitide and temozolomide maintenance therapy in patients with newly diagnosed glioblastoma. *J Clin Oncol* 28(16), 2712-8 (2010) DOI: 10.1200/JCO.2009.26.6650

Abbreviations: AKT, V-akt murine thymoma viral oncogene homolog; CNS, central nervous system; ECM, extracellular matrix; EGFR, epidermal growth factor receptor; ERCC1, excision repair cross complementation 1; GBM, glioblastoma multiforme; IDH, isocitrate dehydrogenase; MDM, murine double mimut; NF, neurofibromatoses; OS, overall survival; p53, protein 53; PDGF, platelet-derived growth factor; PI3K, phosphatidylinositol-3 kinase; PIP3, phosphatidylinositol-3,4,5-triphosphate; PFS, progression-free survival; PTEN, phosphatase and tensin homolog; Rb, retinoblastoma; RGD, arginine-glycine-aspartic acid; TMZ, temozolomide; TSC, tuberous sclerosis complex; VEGF, vascular endothelial growth factor; WHO, World Health Organization

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