Archives of Oncology and Cancer Therapy

ISSN: 2638-5074

Volume 2, Issue 1, 2019, PP: 30-43

Immunotherapy and Glioblastoma Multiforme

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Abstract

GBM is the most common primary brain tumor. As per the World Health Organization (WHO), GBM is classified as grade IV glioma. GBM is invasive and penetrates the adjoining brain tissue. Incidence is higher in case of men and people of white race and non-Hispanic ethnicity. They are common in adults of age range 45-65 years. GBM is a highly aggressive tumor that tends to recur locally. Surgical removal of the tumor is not possible in many cases, as the tumor easily invades its adjacent brain tissue. Progression free survival (PFS) is 6.9 months and overall survival (OS) is 14.6 months for most GBM patients with standard treatment, however, about 3% of cases might live more than 3 years and considered to be long term survivors. The molecular genomics of glioblstoma multiforme cancer has reached advanced stages that enhanced our understanding of its tumorigenesis and presented multiple possible targeted options for its remedy. We review the available drugs and vaccines tested in the management of glioblstoma multiforme. Some has become standard of care, but many are under clinical trials with much anticipated results. In this paper we overview of the class of Monoclonal Antibodies (MAB), Vaccines, Growth Factor Receptor Inhibitors, check point inhibitors, Adoptive T-cell Therapyand kinase inhibitors in the treatment of glioblstoma multiforme.

Keywords: *GBM glioblstomamultiforme, WHO World Health Organization, PFS, Progression free survival, OS overall survival, Monoclonal Antibodies, Growth Factor Receptor Inhibitors, check point inhibitors, Adoptive T-cell Therapy kinase inhibitors.*

Introduction/Epidemiology

GBM is the most common primary brain tumor.[1] Glioma includes all tumors that originate from the glial cells. This include astrocytic tumors [grade I], astrocytoma [grade II], anaplastic astrocytoma [grade III], glioblastoma (GBM) [grade IV] oligodendrogliomas, ependymomas, and mixed gliomas.[2] GBM are generally found in the cerebral hemispheres and spinal cord. As per the World Health Organization (WHO), GBM is classified as grade IV glioma.[3] GBM is invasive and penetrates the adjoining brain tissue.

According to the National Cancer Institute in 2014, it was estimated that there were more than 23,380 new cases diagnosed. Additionally, in the same year, 14,320 cases of death were reported. Incidence is higher in case of men and people of white race and non-Hispanic ethnicity. They are common in adults of age range 45-65 years.[4] Brain and other nervous system cancer represent 1.4% of all the cancers with an age-standardized rate of incidence of 6.4 per 100,000 and mortality rate of 4.3 per 100,000 respectively.[5] From an etiological point of view, different types of environmental exposures and genetic characteristics have been recognized for glial tumors. High incidence countries include Australia, Canada, Denmark, Finland, New Zealand and the US. Regions with a low incidence are Rizal in the Philippines and Mumbai in India.[6]

GBM is a highly aggressive tumor that tends to recur locally. Surgical removal of the tumor is not possible in many cases, as the tumor easily invades its adjacent brain tissue. Progression free survival (PFS) is 6.9 months and overall survival (OS) is 14.6 months for most GBM patients with standard treatment, however, about 3% of cases might live more than 3 years and considered to be long term survivors.[7] GBM are

generally classified into primary and secondary tumors. The type of genetic abnormalities and their sequence is different between these two groups. Incidence rate per 100,000 persons per year for primary and secondary tumors are 2.575 and 0.167, respectively.

Etiology/Predisposing Factors

The precise etiology or risk factor associated with GBM are unknown and are under investigation. Although many factors were identified as potential candidates directly or indirectly through numerous epidemiological studies.

Radiation and Cell Phone Use

Only radiation exposure is directly linked to the development of the GBM. Exposure to ionizing radiation causes excitement of the electron, which causes damage to DNA. Damaged DNA is more prone to cause cell death and necrosis as well as development of tumors. Cell phone emits some non ionizing electromagnetic rays, which increases the risk of incidence of few benign brain tumors, such as low grade gliomas. Patients with prior history of acute lymphoblastic leukemia are prone to brain tumors. Although it is not clearly understood, radiation is still listed as one of the potential risk factors.[8]

Pesticide

Pesticide exposure is not directly linked to the development of GBM, though few epidemiological studies suggested their role in the development of childhood brain tumor.[9]

Head Trauma

Experimental data has shown that trauma is able to act as a carcinogen in the presence of an initiating carcinogen. Researchers hypothesize that when glial cells experience a trauma, they undergo a process called gliosis, in which they experience hypertrophy and multiplication. This is thought to cause a change in the blood-brainand the cerebrovascular architecture of the brain, which could cause the brain to be further exposed to carcinogens or growth factors. This exposure could lead to malignancy and, therefore, GBM.[10]

In 2003, Ranjith K Moorthy et al. presented a case of 56-year-old man who had a history of head injury 5 years prior to CT imaging. He was presented with raised intracranial pressure of 20 days duration. An evidence of posttraumatic gliomas was narrated based on the preliminary diagnostic criteria.[11]

As per the study, in the presence of an initiating carcinogen, trauma can act as a carcinogen. Trauma to glial cell leads to gliosis, which results in hypertrophy and multiplication. Due to the gliosis process, the blood-brain barrier and the cerebrovascular architecture get transformed and leads to exposure to carcinogen.[12]

Alcohol Consumption

According to a collaborative cohort study conducted on 39,766 participants recruited in 1990–1994 and followed up till 2008, it was found thata total 67 glioblastomas were identified during follow-ups. According to the statistics, hazard ratios (HR) were1.16 for each additional 10 grams per day of alcohol intake. As compared to lifetime abstainer, the hazard ratio associated with consumption of alcohol were 1.07 for 1 to 19 g/day, 1.79 for 20 to 39 g/day, 3.07 for 0 to59 g/day and 2.54 for 60 or more g/day. Dose response relationship was suggested for GBM and alcohol consumption.[13]

Diet and Smoking

N-Nitroso compounds were associated as a major cause for the carcinogen production. They were also considered to be responsiblefor brain tumors.[14, 15]

Viruses

SV40, HHV-6, and cytomegalovirus[16] have shown some indirect link withthe GBM development.[17, 18]

Genetic Disorder

It includes neurofibromatosis, tuberous sclerosis, von Hippel-Lindau disease, Li-Fraumeni syndrome and Turcot syndrome. Genetic abnormalities that cause these hereditary clinical syndromes were suggested to be the potential cause of brain tumors, especially GBM.

Pathophysiology and Molecular Basis

The presence of hyperchromatic nuclei and tumor tissues are considered to be the important characteristics of GBM's pathophysiology. Diffused margins can help tumor to invade the adjacent cerebral tissues. Micro vascular proliferation properties nurture the tumor for excessive growth.

Molecular Pathways

Gliomagenesis is caused by various genetic abnormalities and several different oncogenomic events.

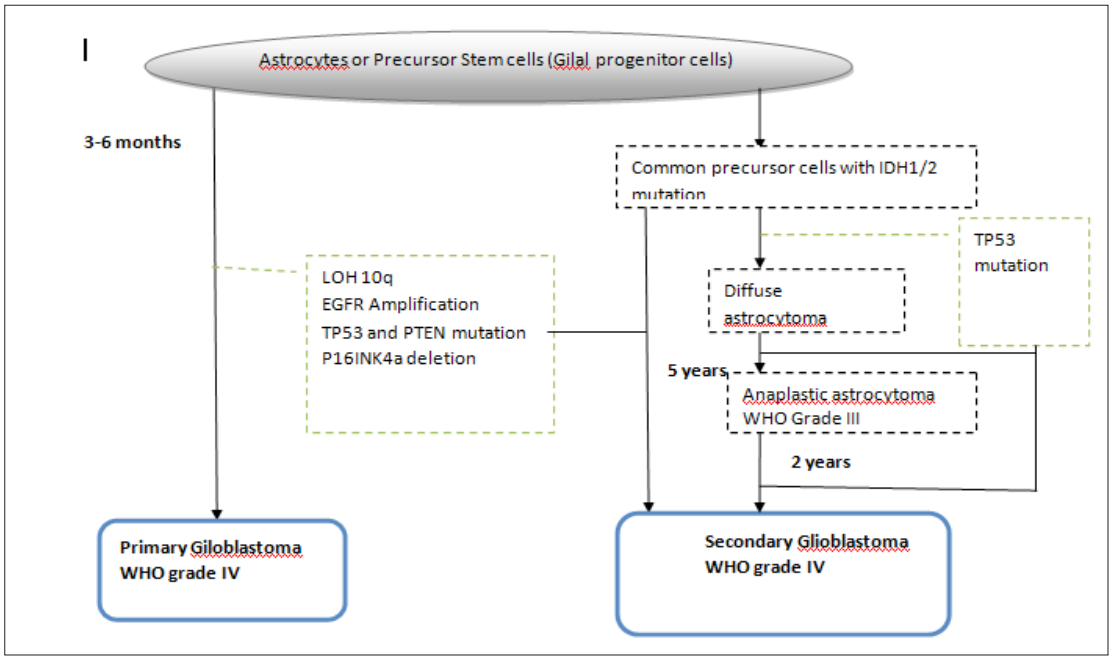

Fig1. *Genetic Pathway for Primary and Secondary Glioblastoma*[19, 20]

Amplification of the epithelial growth factor receptor (EGFR) on chromosome 7

EGFR amplification is commonly seen in 40 to 60% of cases. Growth factor ligands bind to EGFR leading to activation of signaling cascades (production of RAS protein), which alters the transcription of cell process regulation genes in nucleus. EGFR helps in regulating proliferation, cell development, vascularisation and migration within cell. EGFR vIII variation is the most common type of EGFR mutation. When an 801 base pair deletion of exons 2-7 in the EGFR gene leads to EGFR vIII mutation and cause loss of EGFR ligand binding domain, this result in up regulation of EGFR receptor activity and autophosphorylation. It further results in increase in cell proliferation, vascularisation, and increase cellular mortality with resistance to chemotherapy and radiation. Therefore, the prognosis for EGFR vIII mutation is poor and worsens with life expectancy of 0.893 year.

Mutations linked to GBM induction include p16INK4a deletion, p14ARF and p53 mutation, RB1 methylation, and MGMT methylation. These pathways cause mutation in DNA repair mechanism, which include nucleotide excision repair, base excision repair, mismatch repair, and recombination.

p53Pathway

p53 is tumor suppressor gene, which is upregulated in case of cellular stress e.g. DNA damage. When there is cellular stress, p53 gets activated and causes cell cycle arrest and leading to either apoptosis or DNA repair mechanism. A relationship between EGFR and p53 is also established. Negative effects of EGFR mutation is induced because of wild-type functionality of p53.

Entire deletion of chromosome 10 leads to loss of heterozygosity (LOH). This way GBM induction is suggested by deletion of tumor suppressor gene.

Metabolism

Mutation of enzyme isocitrate dehydrogenase 1 is directly linked to the development of glioma. IDH1 encodes for enzyme isocitrate dehydrogenase 1 and glutamate, amino acid and neurotransmitter demands are high in case of IDH 1- mutated glioblastoma. This converts α-ketoglutarate (α-KG) to D-2-hydroxyglutarate (D2HG), a rare metabolite. D2HG, an oncometabolite, inhibits α-KG–dependent enzyme, which helps in cell signaling and epigenetic regulation with collagen synthesis.[21]

Immunotherapy

The primary treatment for GBM is surgical resection. Brain allows and tolerates the introduction of antigen without production of anti-inflammatory reaction. Therefore, application of immunotherapy is very challenging.

Monoclonal Antibodies

FDA Approved Monoclonal Antibodies

Bevacizumab: [22]Bevacizumab is a humanized IgG1 monoclonal antibody, with the ability to bind to vascular endothelial growth factor (VGFR) ligand. VGFR is a tumor associated protein and central mediator of tumor angiogenesis.

Indication and use: Bevacizumab, monoclonal antibody targeting vascular endothelial growth factor receptor has been approved by FDA as a treatment for relapsed/progressive GBM after standard treatment.

PD/PK: Half life of bevacizumab is approximately 20 days (range 11–50days). Time period for attainment of steady state is 100 days.

Contraindication: Known hypersensitivity to bevacizumab is considered a contraindication for its use.

Adverse Events: In clinical trials with bevacizumab for glioblastoma multiforme, the most frequently reported adverse events of any grade were infection (55%), fatigue (45%), headache (37%), hypertension (30%), epistaxis (19%) and diarrhoea (21%). Of these, the incidence of Grade ≥3 adverse events were infection (10%), fatigue (4%), headache (4%), hypertension (8%) and diarrhoea (1%).

Non-FDAApproved Monoclonal Antibodies[23-24]

There are some monoclonal antibodies that are not currently approved by FDA for GBM. However,these agents are under clinical trials in phase I, II, and III as mentioned below:

Rilotumumab: A fully human IgG2 monoclonal antibody directed against the human hepatocyte growth factor (HGF) with potential antineoplastic activity. Rilotumumab binds to and neutralizes HGF, preventing the binding of HGF to its receptor c-Met and so c-Met activation; inhibition of c-Met-mediated signal transduction may result in the induction of apoptosis in cells expressing c-Met. c-Met (HGF receptor or HGFR), a receptor tyrosine kinase overexpressed or mutated in a variety of epithelial cancer cell types, plays a key role in cancer cell growth, survival, angiogenesis, invasion, and metastasis.

Cetuximab: A recombinant, chimeric monoclonal antibody directed against the epidermal growth factor (EGFR) with antineoplastic activity. Cetuximab binds to the extracellular domain of the EGFR, there by preventing the activation and subsequent dimerization of the receptor; the decrease in receptor activation and dimerization may result in an inhibition in signal transduction and anti-proliferative effects. This agent may inhibit EGFR-dependent primary tumor growth and metastasis. EGFR is overexpressed on the cell surfaces of various solid tumors.

Checkpoint Inhibitors

Non-FDA Approved Checkpoint Inhibitors

There are some drugs that are not currently approved by FDA for GBM. However, these drugs are under clinical trials in phase I, II, and III as mentioned in the Table1 below:

Nivolumab: A fully human monoclonal antibody directed against the negative immunoregulatory human cell surface receptor PD-1 (programmed death-1 or programmed cell death-1/PCD-1) with immunopotentiation activity.

Pidilizumab (CT-011): A humanized monoclonal antibody directed against human PD-(programmed cell death 1; PDCD1), with immunomodulating and antitumor activities. Pidilizumab blocks interaction between the receptor PD-1 with its ligands, PD-1 ligand 1 (PD-1L1) and PD-1 ligand 2 (PD-1L2), resulting in the attenuation of apoptotic processes in lymphocytes, primarily effector/memory T cells, and the augmentation of the anti-tumor activities of NK cells. PD-1 is an inhibitory receptor belonging to the B7-receptor family that is expressed on lymphocytes and myeloid cells; its ligands, PD-1L1 and PD-1L2, are expressed not only by hematopoietic cells, but also by cells in non-lymphoid tissues.

Indoximod: Indoximod is major check point inhibitor which is under clinical study. The molecule is also known as 1-methyl-d-tryptophan and is anti immunosuppressive. Indoleamine 2, 3-dioxygenase (IDO) helps in degradation of essential amino acid tryptophan. Indoximod inhibits enzyme indoleamine 2, 3-dioxygenase (IDO) which indirectly regulated the function of T cell by regulating tryptophan. When tryptophan is deleted, T cell gets arrested which in turn immunity is suppressed.

Table1. *Non-FDA Approved Checkpoint Inhibitors*[25-27]

Checkpoint Inhibitors	Clinical trial identifier no.	Phase	Study design	Target antigen
Nivolumab	NCT02017717	Phase III	Randomized Efficacy Study Open Label	anti-PD-1 and anti-CTLA-4 antibodies
Pidilizumab (CT-011)	NCT01952769	Phase I/II	Safety/Efficacy Study, Open Label	PD-1
Indoximod	NCT02052648	I/II	Safety/Efficacy Study Open Label	IDO enzyme

Adoptive T CellTherapy

Non-FDA Approved T Cell Therapy

There are some adoptive T-cells that are not currently approved by FDA for GBM. However, these agents are under clinical trials in phase I, II, and III as in the table-2 below:

Cytomegalovirus (CMV): Immunodominant proteins pp65 and IE1-72 and CMV nucleic acid is highly expressed in case of GBM.[28]

Interleukin-13 receptor alpha 2 (IL13Ra2) are genetically modified autologous central memory-enriched T-cells (Tcm) transduced with a replication-incompetent, self-inactivating (SIN) lentiviral vector. They express a chimeric antigen receptor (CAR), specific for IL13Ra2, enhances tumor cell proliferation, migration to other side with invasive properties which includes cluster of differentiation 137 (CD137; 4-1BB) co-stimulatory signaling domain (it will enhance proliferation of T cell and antitumor activity). They are fused with T cell antigen receptor complex zeta chain (CD3-zeta) signaling domain, human CD19t (it is one of the surface marker to track and measure gene-modified T cells in vivo). It results inthe stimulation of the immune system and anti-neoplastic activity. In the presence of intratumoral administration, IL13Ra2-specifichinge-optimized endogenous Fc receptors (FcRs), helps in prevention of CAR clearance and recognition, 41BB-co-stimulatory CAR/truncated CD19 expressing T-lymphocytes induce toxicity and cytolysis activity in IL13Ra2-expressing tumor cells.

Autologous lymphoid effector cells specific against tumor cells (ALECSAT): A preparation of cytotoxic, autologous lymphoid effector cells, specifically targeted towards tumor cells, with potential immunomodulating and anti-neoplastic activities. The autologous lymphoid effector cells are prepared by drawing a blood sample containing the required precursors for CD4+ helper T-cells, CD8+ cytotoxic T-cells, and natural killer (NK) cells from a cancer patient. The precursor cells are activated, selected and expanded to generate mature autologous lymphoid effector cells with the potential for enhanced tumor recognition. Upon re-administration into the patient, the autologous lymphoid effector cells may induce both humoral and cellular immune responses against tumor cells. This may result in the immune-mediated inhibition of tumor cell proliferation, leading to tumor cell death.

Table2. *Non FDA Approved T Cell Therapy*[29-32]

T cell therapy	Clinical trial identifier no.	Phase	Study design	Target antigen
Intratumoral Infusions of GRm13Z40-2, An Allogeneic CD8+ Cytolitic T-Cell Line Genetically Modified to Express the IL 13-Zetakine and HyTK	NCT01082926	Phase I	Non-Randomized Safety Study Open Label	IL13Rα2
CMV-ALT + CMV-DCs	NCT00693095	Phase I	Randomized Safety/Efficacy Study, Single Blind (Subject)	CMV specific antigen
CAR CMV-specific CTLs	NCT01109095	Phase I	Safety Study, Open Label	HER2
Autologous lymphoid effector cells specific against tumor cells (ALECSAT)	NCT01588769	Phase I	Safety/Efficacy Study, Open Label	Tumor cells

Vaccines

Non-FDA Approved Vaccines

There are few vaccines for GBM that are not currently approved by FDA. However, these agents are under clinical trials in phase I, II, and III as in the Table3 below:

Table3. *Non-FDA Approved Vaccines*[33-50]

Vaccines	Clinical trial identifier no.	Phase	Study design	Target antigen
Rindopepimut (CDX-110)	NCT01498328, NCT01480479	Phase II/III	Randomized Efficacy Study Double Blind	EGFRvIII
DCVax-L	NCT00045968	Phase III	Randomized Efficacy Study Double Blind	T-cell response
ICT-107	NCT01280552	Phase II	Randomized Efficacy Study Double Blind	Autologous dendritic cells pulsed with immunogenic antigens
HSPPC-96	NCT01814813	Phase II	Randomized Open Label	Dendritic cells
autologous tumor lysate-pulsed DC vaccination	NCT01204684	Phase II	Randomized, Safety/ Efficacy Study, Open Label	Autologous Dendritic Cells Pulsed With Tumor Lysate Antigen +/- Toll-like Receptor Agonists
ERC1671/GM-CSF/ Cyclophosphamide)	NCT01903330	Phase II	Randomized Safety/ Efficacy Study Double Blind	(ERC1671/GM-CSF/ Cyclophosphamide) + Bevacizumab vs. (Placebo Injection / Placebo Pill) + Bevacizumab
Dendritic Cell Vaccine	NCT01808820, NCT01902771	Phase I/II	Safety/ Efficacy Study Open Label	Dendritic cell vaccine loaded with tumor lysate
Glioma-associated peptide-loaded dendritic cell vaccine SL-701	NCT02078648	Phase-I/ II	Safety/Efficacy Stydy/Open Label	CTL
Glioblastoma multiforme multipeptide vaccineIMA950	NCT01920191	Phase I/II	Open Label/ Treatment	CTL
BTSC mRNA-loaded DCs	NCT00890032	Phase I	Open Label	autologous brain tumor stem cell messenger ribonucleic acid (mRNA)-loaded dendritic cell vaccine
autologous tumor lysate-pulsed DC vaccination	NCT01957956	Phase I(pilot)	Safety Study Open Label	Allogeneic Tumor Lysate-Pulsed Autologous Dendritic Cell Vaccination
ICT-121 DC vaccine	NCT02049489	Phase I	Safety/ Efficacy Study Open Label	CD133

Vaccines	Clinical trial identifier no.	Phase	Study design	Target antigen
Dendritic cell vaccination, in addition to standard temozolomide chemotherapy and involved field radiation therapy	NCT02010606	Phase I	Non-Randomized Safety Study Open Label	Cancer cells
ADU-623	NCT01967758	Phase I	Non-Randomized Safety/ Efficacy Study Open Label	EGFRvIII-NY-ESO-1 antigens
Montanide ISA-51/survivin peptide vaccine	NCT01250470	Phase I	Safety Study Open Label	survivin peptide vaccine
fusion protein vaccine	NCT01522820	Phase I	Non-Randomized Safety Study Open Label	NY-ESO-1

Active immunotherapy includes application of antigen-presenting cells (APCs), like dendritic cells (DCs) to enhance the antitumor T-cell response.

Rindopepimut: A cancer vaccine consisting of a human epidermal growth factor receptor variant III (EGFRvIII)-specific peptide conjugated to the non-specific immunomodulator keyhole limpet hemocyanin (KLH) with potential antineoplastic activity. Vaccination with rindopepimut may elicit a cytotoxic T-lymphocyte (CTL) immune response against tumor cells expressing EGFRvIII. EGFRvIII, a functional variant of EGFR that is not expressed in normal tissues, was originally discovered in glioblastoma multiforme (GBM) and has also been found in various other cancers such as breast, ovarian, metastatic prostate, colorectal, and head and neck cancers. EGFRvIII contains an 83 amino acid deletion in its extracellular domain and has been shown to transform NIH/3T3 mouse embryonic fibroblast cells in vitro.

Dendritic cell-autologous lung tumor vaccine (DCVax-L): A cancer vaccine consisting of lymphocytes harvested from a patient with lung cancer and induced to become antigen-presenting cells (APCs) known as dendritic cells. The dendritic cells are transduced with the gene encoding an antigen specific to the patient's cancer and then returned to the patient. In the host, the altered cells stimulate the immune system to mount a primary T cell response against lung tumor cells expressing the target antigen. Dendritic cell-autologous lung tumor vaccines have been investigated for use in cancer immunotherapy.

ICT107: It is a dendritic vaccine derived from the patient and targets 6 different antigens. The four antigens are expressed on the surface of cancer stem cells (CSCs).

Vitespen(HSPPC-96): An autologous cancer vaccine derived from tumor-specific gp96 heat shock proteins. Heat shock proteins chaperone peptides through the endoplasmic reticulum, are key regulators of dendritic cell maturation, migration and antigen processing, and are involved in T-cell activation.

Live-attenuated Listeria monocytogenes encoding EGFRvIII-NY-ESO-1 vaccine ADU-623: They are live-attenuated, double-deleted strain of the Gram-positive bacterium *Listeria monocytogenes* (Lm). They encode for mutant form of EGFRvIII and cancer/testis antigen NY-ESO-1. When they are administered to a patient, they encode for EGFRvIII-NY-ESO-1. The vaccine targets dendritic cells, which are highly expressed at EGFRvIII and NY-ESO-1. They upgrade and activate T lymphocytes against EGFRvIII and NY-ESO-1-expressing tumor cells.

Glioma-associated peptide-loaded dendritic cell vaccine SL-701: A cell-based cancer vaccine comprised of dendritic cells (DCs) pulsed with various synthetic glioma-associated antigen (GAA) peptides, with potential antineoplastic activity. Upon subcutaneous administration, the glioma-associated peptide-loaded DC vaccine SL-701 exposes the immune system to various GAA peptides.

This may stimulate both anti-tumoral cytotoxic T lymphocyte (CTL) and antibody responses against the GAA-expressing glioma cells, which may result in tumor cell lysis.

Glioblastoma multiforme multipeptide vaccine IMA950: A cancer vaccine comprising 11 peptides associated with glioblastoma multiforme (GBM), with potential immunomodulating and antineoplastic activities. Vaccination with glioblastoma multiforme multi-antigen vaccine IMA950 stimulates the host immune system to mount a cytotoxic T-lymphocyte (CTL) response as well as a T-helper (Th) immune response against tumor cells expressing these peptides, potentially resulting in decreased tumor growth of GBM. Peptides in IMA950 comprise the following: brevican (BCAN); chondroitin sulfate proteoglycan 4 (CSPG4); fatty acid binding protein 7, brain (FABP7); insulin-like growth factor 2 mRNA binding protein 3 (IGF2BP3); neuroligin 4, X-linked (NLGN4X); neuronal cell adhesion molecule (NRCAM); protein tyrosine phosphatase, receptor-type, Z polypeptide 1 (PTPRZ1); tenascin C (TNC); Met proto-oncogene (MET); baculoviral IAP repeat-containing 5 (BIRC5); and hepatitis B virus core antigen.

Kinase Inhibitors (TKIs)

Non-FDA Approved Kinase Inhibitors

There are some kinase inhibitors that are not currently approved by FDA. However, these agents are under clinical trials in phase I, II, and III as in the Table4 below:

Table4. *Non-FDA Approved Kinase Inhibitors*[51-58]

Drug	Clinical trial identifier no.	Phase	Study design	Target antigen
Dasatinib	NCT00869401	Phase- I/II	Double-blind, Treatment	Src-Protein
Pazopanib	NCT02331498	Phase I/II	Safety/Efficacy Study/Open Label	VEGFR
Gefitinib	NCT00052208	Phase I/II	Safety/Efficacy Study/Open Label	EGFR
Crizotinib	NCT02270034	Phase-I	Open Label/Treatment	Anaplastic Lymphoma Kinase (ALK)
Dovitinib	NCT01972750	Phase-I	Safety Study/Open Label	FGFR3/Receptor Tyrosine kinase
Vandetanib	NCT00821080	Phase-I	Safety Study/Open Label	VEGFR2/EGFR
Erlotinib	NCT00301418	Phase-I	Safety/Efficacy Study/Open Label	EGFR
Buparlisib	NCT01934361	Phase-I/II	Safety/Efficacy Study, Open Label	PI3K

Erlotinib: It isa quinazoline derivative with antineoplastic properties. Competing with adenosine triphosphate, erlotinib reversibly binds to the intracellular catalytic domain of epidermal growth factor receptor (EGFR) tyrosine kinase, thereby reversibly inhibiting EGFR phosphorylation and blocking the signal transduction events and tumorigenic effects associated with EGFR activation.

Pazopanib: It is a small molecule inhibitor of multiple protein tyrosine kinases with potential antineoplastic activity. Pazopanib selectively inhibits vascular endothelial growth factor receptors (VEGFR)-1, -2 and -3, c-kit and platelet derived growth factor receptor (PDGF-R), which may result in inhibition of angiogenesis in tumors in which these receptors are upregulated.

Gefitinib: It is an anilinoquinazoline with antineoplastic activity. Gefitinib inhibits the catalytic activity of numerous tyrosine kinases including the epidermal growth factor receptor (EGFR), which may result in inhibition of tyrosine kinase-dependent tumor growth. Specifically, this agent competes with the binding of ATP to the tyrosine kinase domain of EGFR, thereby inhibiting receptor autophosphorylation and resulting in inhibition of signal transduction. Gefitinib may also induce cell cycle arrest and inhibit angiogenesis.

Crizotinib: An orally available aminopyridine-based inhibitor of the receptor tyrosine kinase anaplastic lymphoma kinase (ALK) and the c-Met/hepatocyte growth factor receptor (HGFR) with antineoplastic activity. Crizotinib, in an ATP-competitive manner, binds to and inhibits ALK kinase and ALK fusion

proteins. In addition, crizotinib inhibits c-Met kinase, and disrupts the c-Met signaling pathway. Altogether, this agent inhibits tumor cell growth. ALK belongs to the insulin receptor superfamily and plays an important role in nervous system development. ALK dysregulation and gene rearrangements are associated with a series of tumors.

Dovitinib: It is a benzimidazole-quinolinone compound with potential antineoplastic activity. Dovitinib strongly binds to fibroblast growth factor receptor 3 (FGFR3) and inhibits its phosphorylation, which may result in the inhibition of tumor cell proliferation and the induction of tumor cell death. In addition, this agent may inhibit other members of the RTK superfamily, including the vascular endothelial growth factor receptor; fibroblast growth factor receptor 1; platelet-derived growth factor receptor type 3; FMS-like tyrosine kinase 3; stem cell factor receptor (c-KIT); and colony-stimulating factor receptor 1; this may result in an additional reduction in cellular proliferation and angiogenesis, and the induction of tumor cell apoptosis. The activation of FGFR3 is associated with cell proliferation and survival in certain cancer cell types.

Vandetanib: An orally bioavailable 4-anilinoquinazoline. Vandetanib selectively inhibits the tyrosine kinase activity of vascular endothelial growth factor receptor 2 (VEGFR2), thereby blocking VEGF-stimulated endothelial cell proliferation and migration and reducing tumor vessel permeability. This agent also blocks the tyrosine kinase activity of epidermal growth factor receptor (EGFR), a receptor tyrosine kinase that mediates tumor cell proliferation and migration and angiogenesis. Check for active clinical trials using this agent.

Dasatinib: An orally bioavailable synthetic small molecule-inhibitor of SRC-family protein-tyrosine kinases. Dasatinib binds to and inhibits the growth-promoting activities of these kinases. Apparently because of its less stringent binding affinity for the BCR-ABL kinase, dasatinib has been shown to overcome the resistance to imatinib of chronic myeloid leukemia (CML) cells harboring BCR-ABL kinase domain point mutations. SRC-family protein-tyrosine kinases interact with a variety of cell-surface receptors and participate in intracellular signal transduction pathways; tumorigenic forms can occur through altered regulation or expression of the endogenous protein and by way of virally-encoded kinase genes.

Buparlisib: An orally bioavailable specific oral inhibitor of the pan-class I phosphatidylinositol 3-kinase (PI3K) family of lipid kinases with potential antineoplastic activity. Buparlisib specifically inhibits class I PIK3 in the PI3K/AKT kinase (or protein kinase B) signaling pathway in an ATP-competitive manner, thereby inhibiting the production of the secondary messenger phosphatidylinositol-3, 4, 5-trisphosphate and activation of the PI3K signaling pathway. This may result in the inhibition of tumor cell growth and survival in susceptible tumor cell populations. Activation of the PI3K signaling pathway is frequently associated with tumorigenesis. Dysregulated PI3K signaling may contribute to tumor resistance to a variety of antineoplastic agents

Growth Factor Receptor Inhibitors

Non-FDA Approved Growth Factor Receptor Inhibitors[59-60]

There are some growth factor receptor inhibitors that are not currently approved by FDA for GBM. However, these agents are under clinical trials in phase I, II, and III as mentioned below:

ABT-414: An epidermal growth factor receptor (EGFR) inhibitor, with potential antineoplastic activity. Upon intravenous infusion, ABT-414 inhibits the activity of EGFR, thereby preventing EGFR-mediated signaling. This may inhibit tumor growth in EGFR-overexpressing tumor cells. EGFR, a receptor tyrosine kinase overexpressed in certain tumor cell types, plays a key role in tumor cell proliferation and tumor vascularization.

Ziv-Aflibercept: A protein comprised of segments of the extracellular domains of human vascular endothelial growth factor receptors 1 (VEGFR1) and 2 (VEGFR2) fused to the constant region (Fc) of human IgG1 with potential antiangiogenic activity. Afilbercept, functioning as a soluble decoy receptor, binds to pro-angiogenic vascular endothelial growth factors (VEGFs), thereby preventing VEGFs from binding to their cell receptors. Disruption of the binding of VEGFs to their cell receptors may result in the inhibition of tumor angiogenesis, metastasis, and ultimately tumor regression.

Autologus Stem Cell Transplantation[61]

This phase I/II trial studies the side effects and best

dose of temozolomide when given together with radiation therapy, carmustine, O6-benzylguanine, and patients' own stem cell (autologous) transplant in treating patients with newly diagnosed glioblastoma multiforme or gliosarcoma. Giving chemotherapy, such as temozolomide, carmustine, and O6-benzylguanine, and radiation therapy before a peripheral stem cell transplant stops the growth of cancer cells by stopping them from dividing or killing them. Giving colony-stimulating factors, such as filgrastim or plerixafor, and certain chemotherapy drugs, helps stem cells move from the bone marrow to the blood so they can be collected and stored. Chemotherapy or radiation therapy is then given to prepare the bone marrow for the stem cell transplant. The stem cells are then returned to the patient to replace the blood-forming cells that were destroyed by the chemotherapy and radiation therapy.

Conclusion

GBM is least expressed till date. Though numerous studies and their results are under investigation, immunotherapy has proven to be effective in the treatment of GBM. Our success in treating GBM is increasing and advancing with the knowledge of the function of the immune system. Researchers are still challenged in exploring innate and adaptive immune systems in this disorder. Immunotherapy has been a promising development in the past few years. The recent activities have increased our understanding of the tumor microenvironment, various immunotherapeutic modalities or combination therapy (like chemotherapy with immunotherapy). Additionally, the effects of such modalities in combination of immunotherapy on cancer patients are still exploratory phase. The complete perspective of immunotherapy treatment has not been realized and/or utilized. Proper preclinical and clinical designs are important pillars in understanding the future of immunotherapy in treating cancer patients.

Abbreviations

GBM glioblstoma multiforme, **WHO** World Health Organization, **PFS** Progression free survival, **OS** overall survival, **MAB** Monoclonal Antibodies, **GFRI** Growth Factor Receptor Inhibitors, **TKI** kinase inhibitors, **EGFR** epidermal growth factor receptor, **VGFR** vascular endothelial growth factor receptors, **HGF** hepatocyte growth factor, **PD-1** (programmed death-1**, PD-1L1** PD-1 ligand 1, **PD-1L2** PD-1 ligand 2, Indoleamine 2, 3-dioxygenase **IDO,** chimeric antigen receptor **CAR**, Fc receptors **FcRs**, Autologous lymphoid effector cells specific against tumor cells **ALECSAT,** antigen-presenting cells **APCs,** keyhole limpet hemocyanin **KLH**, cytotoxic T-lymphocyte **CTL**, antigen-presenting cells **APCs**, Listeria monocytogenes **Lm**. dendritic cells **DCs**, glioma-associated antigen **GAA**, **CTL** cytotoxic T lymphocyte. **TH** T-helper protein tyrosine phosphatase, receptor-type, Z polypeptide 1 **PTPRZ1**, tenascin C **TNC**, Met proto-oncogene **MET**; baculoviral IAP repeat-containing 5 **BIRC5**, brevican **BCAN**, chondroitin sulfate proteoglycan 4 **CSPG4**; fatty acid binding protein 7, brain **FABP7**, insulin-like growth factor 2 mRNA binding protein 3 **IGF2BP3**; neuroligin 4, X-linked **NLGN4X,** neuronal cell adhesion molecule **NRCAM**, anaplastic lymphoma kinase **ALK** c-Met/ hepatocyte growth factor receptor **HGFR**., **PD-1**: programmed death-1, **PD-L1**: programmed death-ligand 1, **Vss**: steady-state volume of distribution, **Ig**: Immunoglobulin, **APCs**: antigen presenting cells, **CTLs**: cytotoxic T-lymphocytes, **CTLA4**: cytotoxic T-lymphocyte-associated antigen-4, **Fc**: fragment constant, **CDC**: complement-dependent cytotoxicity, **TAAs**: tumor-associated antigens, **LAG-3**: lymphocyte activation gene-3, **TILs**: tumor-infiltrating lymphocytes, **MHC**: major histocompatibility complex, **IgSF**: immunoglobulin superfamily, **HLA**: Human Leukocyte Antigen.

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Citation: **Timothy Allen, MD, Ph.D.** *Immunotherapy and Glioblastoma Multiforme. Archives of Oncology and Cancer Therapy. 2019; 2(1): 30-43.*