

Novel therapies for high-grade gliomas: A vision for future

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ABSTRACT

The treatment for high-grade glioma remains an enigma. The standard treatment using surgery, radiation therapy and chemotherapy for such highly malignant lesions has only yielded modest results, in terms of survival and improving the quality of life of patients. Less than 10% of such patients survive beyond two years. All conventional therapies have failed to increase the survival beyond this extent. There has been a growing interest in the molecular approaches for the treatment of high-grade gliomas which include gene therapy, oncolytic virotherapy, and immunotherapy. These new therapies are in preclinical and investigational stages. They may not substitute the conventional therapies; they may not be the ultimate elixir for this deadly disease. However, in the coming years, they are likely to have synergistic and complimentary roles alongside conventional therapies. Through this paper, we have attempted to highlight the rationale behind gene therapy which can be used for cytotoxic approaches, immunomodulation strategy, and targeted toxin delivery in the tumor cell. We have reviewed current available literature and through this paper focus on reporting such therapeutic options, their potential usage, benefits and limitations.

Key words: Current studies, gene therapy, malignant glioma, novel therapy

INTRODUCTION

The most common primary brain tumor is glioblastoma multiforme (GBM), which is a highly malignant neoplasm, with a median survival of around 12–18 months post diagnosis.^[1-3] The current accepted protocol for treatment involves surgical excision followed by adjuvant chemotherapy and radiotherapy.^[3] Gamma knife (GK) and temozolamide, in recent times, have added a new dimension to glioma treatment, even these modalities have not been able to bring a paradigm shift in overall survival and morbidity. Novel therapeutic strategies are needed to tackle such a highly malignant cancer. Gene modulation strategies might not be the ultimate elixir for this highly malignant cancer, but they have shown some promise. We have reviewed the literature and present a simplistic view, which can help a neurosurgeon in understanding and remaining abreast with the current knowledge on the subject.

The treatment of high-grade glioma can be divided into two major categories: initial treatment and treatment

at recurrence. Promising therapies are first tested in recurrent cases where there are no proven alternatives and they can be combined with external beam radiotherapy and temozolamide which are considered as a standard of care.^[4]

Alkylating Agents

One common mode of resistance to temozolamide (alkylating agent) is by an enzyme encoded by the MGMT gene, O⁶-alkylguanine – DNA alkyltransferase. Methylation of the promoter region of the gene silences it, thus increasing the sensitivity to temozolamide.^[4] Another mechanism of resistance is by the poly (adenosine di-phosphate –ribose) polymerase (PARP) system; a number of PARP inhibitors have been developed and are being analyzed for their feasible use along with RT and temozolamide therapy.^[4] Strategies to overcome resistance may include more frequent dosing schedules for temozolamide, known as dose intense schedules.^[6] Direct enzyme inhibition by O⁶-benzylguanine, which has been used in combination with temozolamide as one more tactic to overcome the resistance.^[5]

Molecular Targeted Therapies

These novel therapeutic strategies are designed to address the common problem with high-grade gliomas which include uncontrolled cellular proliferation, decreased apoptosis, invasion and angiogenesis. During the malignant progression of gliomas, many tumor suppressor genes are inactivated while growth factors and

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oncogenes are overexpressed.^[7] Thus, aim of such therapy is to prevent “gain of function” genes (oncogenes) or to replace “loss of function” of few genes (tumor suppressor genes). The majority of targeted agents are small molecule tyrosine kinase inhibitors or monoclonal antibodies.^[8] Other targeted sites for interference are angiogenesis pathway, tumor growth factor pathways and intracellular signaling pathways [Figure 1]. Prodrug activation using microbial genes or *ex vivo* transfection of autologous tumor cells for producing cytokines or other immunomodulatory genes can be other methods for producing molecular interference and preventing glioma growth.

Induction of Apoptosis

p-53 gene

This gene's abnormality is known to occur in majority of high-grade gliomas, although it is seen to be mutated in around 30% cases.^[7] Kim *et al.*^[9] had reported that multiple gene replacements with concurrent exposure to adenovirus containing p53 gene can have additive effects in the treatment of glioma cell lines.

Rb gene

Retinoblastoma gene is a tumor suppressor gene and in 30% malignant glioma abnormalities of this gene are found associated.^[10] Inactivation of this gene leads to tumor progression; therefore, restoration of wild type retinoblastoma activity in such tumors through vector delivery gene therapy may provide another therapeutic option.^[7]

TRAIL receptors

The tumor necrosis factor (TNF) receptor super family is a group of receptors that have a significant role in cell survival, division, differentiation and death.^[11] A subfamily of the TNF receptor super family are death receptors which are distinguished by the presence of a conserved intracellular motif called the death domain that can activate apoptosis.^[11] Glioma and other brain tumors are known to express similar death receptors like Fas receptor or TRAIL receptors.^[12] Cytotoxicity *in vitro*, in glioma cell lines by infected viral vectors expressing either Fas ligand or TRAIL have been studied.^[13,14] However, usefulness of these two is yet to be demonstrated on humans.^[11]

Miscellaneous Other Genes Associated with Apoptosis

Genes like Bcl-2, Bax, gas-1, NF-kappaB, p73alpha, Apaf-1, Caspase 3, Caspase 9, Bcl-X(L) are under study for feasibility of use in glioma therapy.^[7] Their adenoviral vector-mediated delivery may prove beneficial.

SIGNAL TRANSDUCTION INHIBITORS

Growth factors like epidermal growth factor (EGF) and their respective receptors regulate proliferation

and survival pathways, EGF is known to be involved in pathogenesis of various human malignancies.^[15,16] Over expression of EGF- receptor (EGFR) is known to occur in nearly half of glioblastomas;^[17] this also portends a poorer prognosis because of increased aggressiveness of GBM and radiation resistance due to changes in EGFR signaling.^[15] Drugs like Gefitinib (Iressa®; Astra-Zeneca Pharmaceuticals, Wilmington, DE) is a molecular inhibitor of the EGFR [Figure 2]. 13% of patients with recurrent GBM were seen to have progression-free survival for a minimum period of six months in a phase II trial using Gefitinib as a monotherapy.^[18] Another drug Erlotinib (Tarceva®, OSI Pharmaceuticals, Inc., Melville, NY) is an inhibitor of the EGFR which also inhibits active mutant EGFRvIII found in approximately 40% of GBMs.^[17,19] Initial trials with Erlotinib have not produced uniform results.^[20] Phosphorylated protein

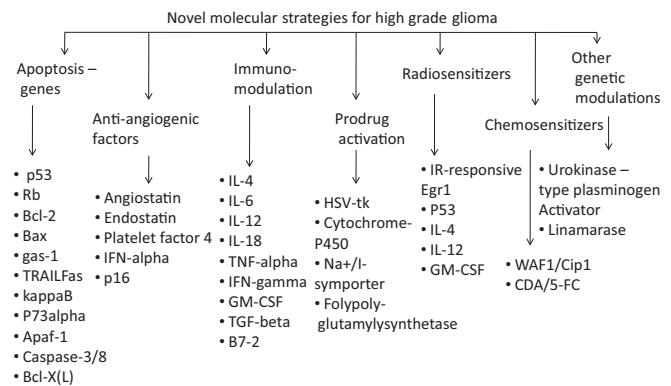


Figure 1: Shows multiple sites of interference that are being tried currently for control of high grade glioma

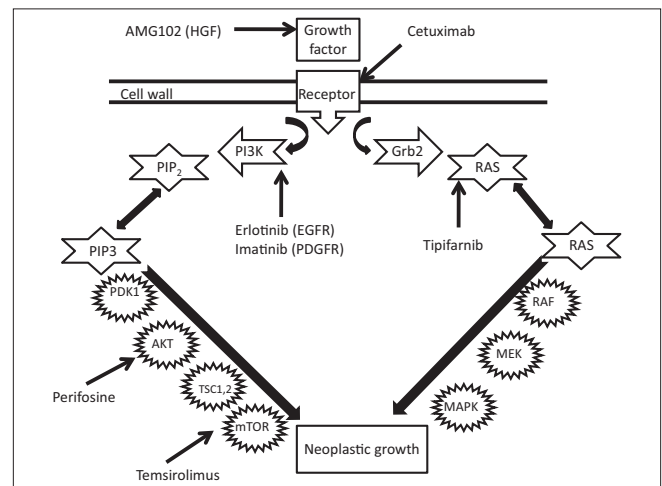


Figure 2: Diagram showing growth factor pathways with targets for newer gene therapy agents. EGFR indicates epidermal growth factor receptor; Grb2, growth factor receptor-bound 2; HGF, hepatocyte growth factor; MAPK, mitogen-activated protein kinase; MEK, MAPK kinase; mTOR, mammalian target of rapamycin; PDGFR, platelet-derived growth factor receptor; PDK, phosphatidylinositol-dependent kinase; PI3K, phosphoinositide-3 kinase; PIP2, phosphatidylinositol 4,5-bisphosphate; PIP3, phosphatidylinositol 3,4,5-triphosphate; TSC, tuberous sclerosis complex

kinase B can be a cause for resistance to EGFR inhibitors. Drugs with dual tyrosine kinase inhibiting potential may overcome this potential resistance. AEE788 (Novartis Pharmaceuticals Corporation, East Hanover, NJ), EGFR and vascular endothelial growth factor (VEGF) receptor (VEGFR) inhibitor lapatinib (GW-572016; GlaxoSmith-Kline, Philadelphia) are the two examples of such drugs.^[17,21,22]

Bevacizumab is a human recombinant monoclonal antibody specific for the VEGF ligand. VEGF is highly expressed by glioblastoma cells which have a hypoxic, acidic microenvironment due to abnormal vascularization and this causes resistance to treatment.^[23] This drug is approved in USA and Europe for the treatment of metastatic breast cancer, colon cancer and non-squamous lung cancer. Kreisl *et al.*,^[24] in a phase II trial on 48 patients of recurrent glioblastoma had reported six-month, progression-free survival (PFS) as 29% and concluded that single-agent bevacizumab has significant biologic and anti-glioma activity in patients with recurrent GBM. Friedman *et al.*,^[25] also in a phase II trial on bevacizumab alone and in combination with irinotecan in recurrent GBM, reported six-month PFS of 42.6% in Bevacizumab group and 50.3% PFS in bevacizumab plus irinotecan group. They also reported usefulness of Bevacizumab alone or in combination with irinotecan in recurrent glioblastoma.

Imatinib mesylate (Gleevec®, Novartis Pharmaceuticals Corporation) is a small molecule inhibitor of the Bcr-Abl receptor, tyrosine kinase which has inhibitory effects on platelet-derived growth factor receptor (PDGFR) [Figure 2]. Upregulation of this receptor is also seen in GBM.^[20] Reardon *et al.*^[26] in a phase II clinical trial on imatinib plus hydroxyurea in recurrent GBM has concluded that it was well tolerated among patients with recurrent GBM but did not show clinically meaningful anti-tumour activity. Razis *et al.*,^[27] found that intact imatinib was detected in GBM tissue but proliferation of tumor and survival mechanisms are not substantially reduced by imatinib therapy in most patients. Imatinib can increase the cytotoxic effect of ionizing radiation in a human GBM cell line.^[28]

Cetuximab, which is an antibody for EGFR receptor, is also being studied in early phase clinical trials.^[4]

RAS/RAF/mitogen-activated protein kinase pathway. RAS protein constitutes another second messenger pathway that is activated by EGFR and PDGFR. This commences signaling cascades and includes mitogen activated protein kinase that has a role in cell proliferation.^[4] Farnesyl transferase inhibitors inhibit enzyme that activates RAS [Figure 2]; Tipifarnib

(R115777) is an example of that, which is shown to have modest activity as a single agent.^[29]

Hepatocyte growth factor (HGF)/scatter factor binds with c-MET receptor, activating intracellular signaling cascades like EGFR and PDGFR. AMG102 is a human monoclonal antibody against this hepatocyte growth factor which is currently in phase 2 study.^[4]

Phosphoinositide 3 kinase (PI3K)/AKT pathways/mammalian target of rapamycin pathway. Phosphoinositide-3 kinase (PI3K) pathway is another intracellular second messenger pathway activated by EGFR, PDGFR or c-MET receptor. This PI3K activates AKT also known as protein kinase B and many other targets which also include the mammalian target of rapamycin. Phosphate and tensin homologue (PTEN) is the main negative regulator for this above pathway and mutation of this *PTEN* gene or loss of heterozygosity of the chromosome on which it is present can lead to over activity of this pathway in GBM patients. Temsirolimus and everolimus are both inhibitors of the mammalian targets of rapamycin [Figure 2].^[4] Temsirolimus as monotherapy has shown little efficacy in recurrent GBM.^[30]

Other inhibitors which are under consideration include CP-673,451 (Pfizer pharmaceutical, New York) which inhibits PDGFR- β , insulin like growth factor receptor (IGFR), transforming growth factor-beta (TGF- β) and heat shock protein 90 (HSP-90).^[17,20]

Epigenetic alteration: Vorinostat, which is a histone deacetylase inhibitor, plays a role in the chromatin structural organization of DNA and has shown modest benefit as a single agent in GBM.^[31]

The potential for greater effectiveness by inhibiting multiple pathways is counterbalanced by the corresponding increase in the risk of side effects from systemic inhibition of these same pathways.^[4]

VIROTHERAPY

Oncolytic virus replication in the neoplastic cells can cause tumor lysis. To achieve safe and effective oncolytic activity and prevent toxicity to normal brain tissue, targeted delivery of oncolytic vector and its replication within the tumor cells is required.^[2] Numerous virus species have been studied for this purpose, but Herpes Simplex Virus (HSV) vectors are the most commonly used ones for glioma therapies. Oncolytic vectors are classified as either mesogenic or lentogenic. Mesogenic vectors are moderately pathogenic, capable of producing viable progeny and infecting adjacent cells while lentogenic vectors are in contrast attenuated non pathogenic,

producing defective progeny and incapable of spreading between the tissues.^[32] Viruses in oncotherapy have two important roles: first, as vectors for therapeutic gene delivery and second, as genetically engineered infectious agents capable of selectively lysing tumor cells.^[33]

HSV vectors: The most extensively studied oncolytic HSV vector is G207, which is a genetically engineered HSV-1. As a result of this, it can only replicate in fast dividing cells. The delivery of G207 can be combined with prodrugs like ganciclovir to further increase its oncolytic effects.^[2] HSV virus can also be genetically engineered to encode transgenes like extracellular fragment of brain specific angiogenesis inhibitor 1,^[34] shRNA specific for VEGF,^[35] angiostatic transgenes like platelet factor -4,^[36] immunostimulators like IL-4^[37] or cytotoxic agents like TNF α .^[2,38]

Adenovirus vectors: Adenovirus can also be genetically engineered to selectively replicate and cause oncolysis. ONYX-015, Ad4-Delta24 and Ad5-Delta24RGD are the three widely studied oncolytic adenoviruses.^[2] ONYX-015 has the ability to replicate in p53 defective tumor cell, Ad5-Delta24 can bind with the retinoblastoma (Rb) protein, while RGD motif of Ad5-Delta24RGD provides it affinity for α_v integrins present in rich numbers in glioma cells. Use of adenovirus to target glioma specific promoters like nestin, human telomerase reverse transcriptase (hTERT), GFAP and survivin are also described.^[2]

Measles and Reovirus vectors: Forsyth *et al.*^[39] reported that Reovirus is an oncolytic virus with activity *in vivo* models of malignant gliomas. They found that intratumoral administration of the genetically unmodified reovirus was well tolerated. Msaouel *et al.*,^[40] reported that strains of the attenuated measles virus Edmonston (MV-Edm) vaccine lineage can preferentially infect and destroy malignant cells while not harming the surrounding normal tissue. This is because of overexpression of measles virus receptor CD46 by tumor cells. To help *in-vivo* monitoring of viral gene expression and replication, these strains can be engineered to express peptides, like thyroidal sodium symporter (NIS) gene (MV-NIS) which can help in imaging or soluble marker peptides like carcinoembryonic antigen (CEA;MV-CEAvirus).

IMMUNOTHERAPY

It is a well-known fact that oncogenesis is linked with immune suppression because a normal, noncompromised immune system has the ability to clear transformed neoplastic cells. This is mediated by natural killer (NK) cells and also by cytotoxic T cells.^[41] Neoplastic cells with ability to bypass this immune surveillance are able to

form larger tumors. Gliomas have significant ability to weaken the immune function.^[42] Gliomas are known to cause decreased T-cell responsiveness to tumor antigens, decreased T-cell receptor mediated signaling, leucopenia, depressed antibody synthesis, impaired antigen presenting cell(APC) function.^[43] It is believed that secretion of factors like tumor growth factor beta (TGF- β), interleukin-10 (IL-10), prostaglandin E₂ (PGE₂), certain gangliosides and may be an unidentified glioma secreted soluble factor are responsible for this immunosuppressive behavior of gliomas [Figure 3].^[43]

It is postulated that boosting this impaired immune responsiveness to gliomas can help in their eradication. These immunotherapy approaches can include adoptive immunotherapy (in which passive administration of sensitized immune cells is done), passive immunotherapy (exogenous antibodies which are target specific are given), and active immunotherapy (with tumor vaccines).^[20]

Inducing an effective immune response is still a challenge because of paucity of antigen presenting dendritic cells in the brain, lack of lymphatic outflow within brain which can allow dendritic cells to exit brain, presence of immunosuppressive regulatory T cells and immunosuppressive cytokines like TGF β .^[2,44-46] Myeloid derived suppressor cells have recently been described in human GBMs and are also attributed to cause immunosuppression.^[47]

Passive Immunotherapy

Possibility of developing antibodies targeting specifically tumor cells provided new hope in the treatment of neoplastic cells and sparing the normal tissue. Theoretically, it is believed that an antibody designed against a cell surface antigen present specifically on the tumor cell can be conjugated with a toxic payload which can thereby deliver this to tumor tissue only. The example of such conjugation is Cotara® (Peregrine

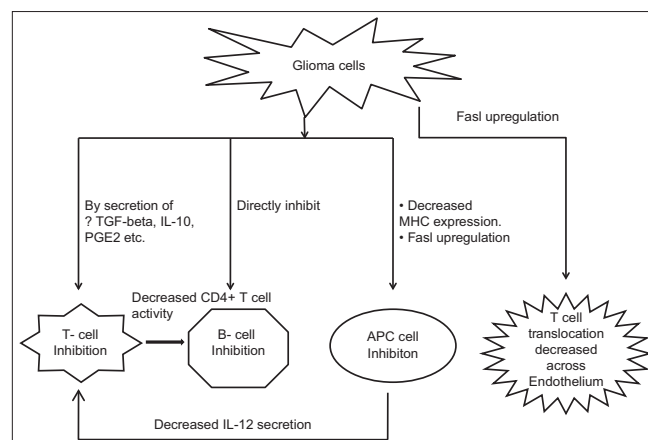


Figure 3: Role of various immunomodulators in glioma tumorigenesis

Pharmaceuticals, Inc.), which is an investigational treatment for GBM that links a radioactive isotope to a targeted monoclonal antibody designed to bind to the DNA histone H1 complex that is exposed by dead and dying cells found at the center of solid tumors. Cotara is administered as a single-infusion therapy directly into the tumor using convection-enhanced delivery (CED), it destroys the tumor from the inside out by binding to the dying tumor cells and delivering its radioactive payload to the adjacent living neoplastic cells, with minimal exposure to normal tissue. The catheters for CED are placed under neuronavigation guidance. We have participated in a phase II clinical trial of this drug and encouraging results have been reported from our center.

The problem associated with this approach of developing antibodies against tumor cells is that many antigens that are found to be up regulated in the tumor cells are expressed on the normal tissue as well and thus normal cells also are at risk. Moreover, this tumor specific antigen needs to have constancy of expression and a minimum density of $\geq 1 \times 10^{15}$ molecules per tumor cell in order to achieve any significant therapeutic effect.^[48]

Some of the antigens targeted for glioma therapy are epidermal growth factor receptor (EGFR),^[49,50] tenascin,^[51,52] neural cell adhesion molecule,^[53] glioma-associated antigen,^[54,55] chondroitin sulfate proteoglycan.^[53]

ADOPTIVE IMMUNOTHERAPY

This approach refers to potential transfer of tumoricidal T-cells into patients with glioma. Systemic infusion or local intracerebral inoculations as a means to deliver these cells have been tried.^[43] Much hope was pinned to IL-2 (interleukin 2) which was identified as a potent T-cell growth factor and LAK cell based, which are peripheral lymphocytes capable of lysing NK cell resistant tumor targets, were developed.^[56]

Apart from Hayes *et al.*,^[57] who reported encouraging results, Barba *et al.*,^[58] and Merchant *et al.*,^[59] have not been able to support its success. The problem with this approach is that generation of tumor specific T-cell clones is questionable because now it is known that antigen specific T-cell activation occurs from multitude of reasons, which not only involve T-cell receptor (CD3 antigen) but also co-stimulatory signals that can be provided by professional antigen presenting cells.^[43]

CYTOKINE THERAPY

Much research is focused on cytokines involved in the stimulation of antitumor T-cell activity which include

IL-2, IL-4, IL-12 and interferons (IFN- α , β , and γ). Tumor necrosis factor (TNF- α) enhance immunogenicity and can induce apoptosis.^[43] Transgenes encoding for highly toxic proteins like *Pseudomonas* exotoxin can be delivered using non-replicating first generational adenoviral vectors. Cytotoxicity of this approach can be restricted by linking this PE toxin to human IL-13.^[2] A variant of IL-13 receptor is overexpressed on GBM cells^[60] and this differs from its counterpart IL4R/IL13R which is expressed in normal tissues.^[61] Cintredekin Besudotox which is a protein formulation of this targeted toxin was studied in phase I–III trials, but had problems like need for multiple injections or continued injections to achieve therapeutic effects due to short half life.^[62–64] Applicability of such approaches to humans is limited because of sub therapeutic half life and toxicity. However, recently, encouraging pre-clinical experiments in human GBM xenografts have been reported by adenoviral vector mediated delivery of mIL-13-PE causing tumor regression and long-term survival in around 70% of the animals without much toxicity.^[2]

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