

Innovative therapies for malignant brain tumors: the road to a tailored cure

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Abstract. *Background:* Immune tolerance, immune escape, neoangiogenesis, phenotypic changes, and glioma stem cells are all responsible for the resistance of malignant brain tumors to current therapies and persistent recurrence. The present study provides a panoramic view of innovative therapies for malignant brain tumors, especially glioblastoma, aimed at achieving a tailored approach. *Methods:* PubMed/Medline and ClinicalTrials.gov were the main sources of an extensive literature review in which “Regenerative Medicine,” “Cell-Based Therapy,” “Chemotherapy,” “Vaccine,” “Cell Engineering,” “Immunotherapy, Active,” “Immunotherapy, Adoptive,” “Stem Cells,” “Gene Therapy,” “Target Therapy,” “Brain Cancer,” “Glioblastoma,” and “Malignant Brain Tumor” were the search terms. Only articles in English published in the last 5 years were included. A further selection was made according to the quality of the studies and level of evidence. *Results:* Cell-based and targeted therapies represent the newest frontiers of brain cancer treatment. Active and adoptive immunotherapies, stem cell therapies, and gene therapies represent a tremendous evolution in recent years due to many preclinical and clinical studies. Clinical trials have validated the effectiveness of antibody-based immunotherapies, including an in-depth study of bevacizumab, in combination with standard of care. Pre-clinical data highlights the role of vaccines, stem cells, and gene therapies to prevent recurrence. *Conclusion:* Monoclonal antibodies strengthen the first-line therapy for high grade gliomas. Vaccines, engineered cells, stem cells, and gene and targeted therapies are good candidates for second-line treatment of both newly diagnosed and recurrent gliomas. Further data are necessary to validate this tailored approach at the bedside. (www.actabiomedica.it)

Keywords: Cell-based Therapy; Glioblastoma; Immunotherapy Malignant Brain Tumor, Target Therapy.

Background

Treatment of malignant brain tumors remains one of the greatest challenges in oncology.

Glioblastoma (GBM) represents 60%–75% of primary malignant brain tumors[87] and has an annual incidence rate of 3–4 cases/100,000 people each year[18,56].

Despite primary multimodal management with gross total surgical resection followed by chemoradiotherapy, GBM still has a dismal prognosis with a

median survival of 12–14 months and a 5-year overall survival rate of less than 10%[80,79].

The relative lack of success of treatment revealed the necessity for innovative techniques. GBM therapy resistance is attributable to high rates of cell growth and angiogenesis, intrinsic heterogeneity, the presence of glioma stem cells, and many molecular mechanisms associated with anomalous signaling pathways that recognize and adapt to ongoing threats[25,3,72].

Progress in genetic studies, identification of molecular abnormalities, and advances in regenerative

medicine offer new insights for the development of new therapeutic strategies tailored to specific molecular targets in different pediatric and adulthood central nervous system (CNS) pathologies[61,75,21,23,55,60,73].

Regenerative medicine is a broad field that encompasses a range of bioengineering approaches and advanced therapy medicinal products; among these, cell-based therapy is one of the most attractive therapeutic platforms[53,44].

The aim of this study was to summarize innovative therapies for malignant brain tumors. The most recent advances in chemotherapy (i.e., targeted molecular agents, virotherapy, engineered cells, and stem cell-based and gene therapies) are discussed in detail, also focusing on the future challenges of a tailored approach.

Methods

A comprehensive literature review was conducted using PubMed/Medline search engine with combinations of Medical Subject Heading (MeSH) terms and text words.

The MeSH terms “Regenerative Medicine,” “Cell-Based Therapy,” “Chemotherapy,” “Vaccine,” “Cell Engineering,” “Immunotherapy, Active,” “Immunotherapy, Adoptive,” “Stem Cells,” “Gene Therapy,” and “Target Therapy” were used. They were combined with further MeSH terms: “Brain Cancer,” “Glioblastoma,” and “Malignant brain tumor.”

Our research included articles for a historical review of CNS tumor therapy and then focused on articles on novel therapeutic approaches and emerging techniques. The results were further filtered based on their titles and abstracts to sort the most relevant articles, and a descriptive analysis was performed.

The limits used included a publication period of 2015–2020 and articles published in the English language or translated to English and pertinent to neuro-oncology.

Results

Cell-based therapies

Cell-based therapies represent a new frontier for the treatment of malignant CNS tumors. This new

therapeutic approach has been tested in many clinical trials and has demonstrated its enormous validity in combination with conventional surgery and radiotherapy (RT). Advanced cell-based therapies are categorized according to the type of medicinal product involved. This technology-based classification for treatment of GBM includes the somatic cell, gene modification, and genome editing[53].

1 Somatic cell therapies

This approach involves propagated or differentiated human cells that were autologous, allogenic or xenogenic[45], purified, and administered for therapeutic purposes. Somatic cell technologies include two forms of treatment: immunotherapy and stem cell-based therapy[53].

1.1 Immunotherapies

The rationale for the use of immunotherapy to treat malignant brain tumors is supported by evidence of a better prognosis together with a high level of expression of tumor-infiltrating lymphocytes and CD8+ and CD4+ T helper and regulatory T cells (Tregs)[52]. Immunotherapy is active (checkpoint inhibitors and vaccines) or adoptive (engineered T or NK cells)[53].

1.1.1 Active immunotherapies

1.1.1.1 Checkpoint inhibitors

Checkpoint inhibitors are at the forefront of the immunotherapy revolution, with real survival benefits in multiple solid tumors. They are categorized as chemotherapy drugs, which carry out their function in specific stages of the cell cycle, or antibody-based therapies.

Alkylating agents

First-line treatment is based on temozolomide (TMZ, Temodar®), an oral alkylating agent with 100% bioavailability and the ability to cross the blood-brain barrier due to its lipophilic properties. TMZ modifies DNA or RNA via alkylation of guanine and adenine and causes mismatched base pair, G2 phase arrest, and cell apoptosis. The activity of TMZ closely depends on DNA

repair programs, such as O6-methylguanine-DNA methyltransferase (MGMT), a demethylating enzyme. MGMT expression influences the efficacy of TMZ, and methylation of the MGMT gene, which is located on chromosome 10q26, is a strong predictor of tumor sensitivity and better outcomes after treatment[93,59,32].

The major limit of TMZ is rapid *in vivo* hydrolytic degradation, which requires frequent and massive doses, increasing the risk of potential adverse effects. Several recent studies tested the possibility of combining conjugate TMZ with polymer scaffold molecules to prevent its rapid clearance and improve tumor uptake and antitumor activity. In 2015, Fang et al. demonstrated that the conjugation of TMZ with copolymers (a polyethylene glycol-chitosan graft) increased the TMZ half-life and incorporation into tumor-targeting cells[20].

For patients with evidence of tumor progression after first-line treatment, second-line treatment includes a TMZ re-challenge or PCV regimen, which consists of procarbazine, lomustine (1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea; CCNU), and vincristine. Despite the approval of these therapies for recurrence, there are insufficient clinical trials demonstrating sufficient therapeutic effectiveness[76].

Many phase III clinical trials have also demonstrated the efficacy of 1,3-bis(2-dichloroethyl)-1-nitrosourea (BCNU, carmustine, Gliadel®) wafers, a biodegradable polymer containing a chemotherapeutic agent, implanted during surgery at the tumor site to locally provide a therapeutic dose of BCNU. This technique, combined with RT and systemic TMZ, increases survival by 8 weeks[2,54].

Antibody-based therapies

Antibody-based therapies aim to overcome the ability of GBM to escape the immune response, remaining effective against the tumor.

The therapy is based on human monoclonal antibodies (MAbs) that directly target specific molecular ligands to interrupt aberrant cellular pathways and activate the antitumor immune cascade.

A milestone agent in this group is bevacizumab (Avastin®), a MAb that targets vascular endothelial growth factor A (VEGF-A), which blocks the action of VEGF and inhibits angiogenesis, counteracting tumor growth. Bevacizumab has been tested in some

clinical trials, and it is currently approved in addition to RT and adjuvant TMZ for recurrent disease, showing significant improvements in survival[17,36] (<https://www.clinicaltrials.gov/#NCT00501891>).

Concurrent use of irinotecan, a chemotherapeutic agent that inhibits topoisomerase I, and bevacizumab has shown a synergistic effect in phase II trials with a 6-month increase in survival[29].

The best studied immuno-targets include programmed cell death protein 1 (PD-1) and its ligand, PD-L1, cytotoxic T-lymphocyte antigen 4 (CTLA-4), T cell immunoglobulin and mucin domain 3 (TIM-3), and indoleamine 2,3-dioxygenase-1 (IDO1).

The PD-1 receptor is expressed on activated immune cells, and their ligands, PD-L1 and PD-L2, are expressed on the surface of dendritic cells and macrophages. Physiologically, the PD-1/PD-L1 interaction promotes immune cell regulation, triggering the apoptosis of T cells and minimizing chronic autoimmune inflammation. PD-L1 overexpression on GBM cells with PD-1/PD-L1 upregulation is a system of immunity evasion in the tumor microenvironment as negative feedback for T cells to inhibit the activity of cytotoxic CD8+ lymphocytes[91,10].

Nivolumab, a human IgG4 subtype targeting PD-1, has been tested for its safety and efficacy in phase II and III clinical trials and was also combined with bevacizumab (<https://www.clinicaltrials.gov/#NCT03890952>). In addition, many anti-PD-1 antibodies (pembrolizumab and cemiplimab) and anti-PD-L1 agents (atezolizumab[43], avelumab, and durvalumab[4]) have also been approved for GBM.

CTLA-4 is an inhibitory receptor on the surface of T cells that binds the CD80 and CD86 ligands on antigen cells to downregulate T cell activity. Ipilimumab, a human monoclonal IgG1 antibody for CTLA-4, is the standard therapy for metastatic melanoma and is used in combination with PD-1 inhibitors and other immunotherapies for recurrent GBM[41,57].

Recent studies have investigated the development of antibodies against TIM-3[13,33], a surface receptor expressed on CD4+ and CD8+ T cells, and IDO1, an intracellular enzyme, which are both involved in T cell exhaustion in GBM[66,95].

Several MAbs, such as anti-EGFR agents (cetuximab and nimotuzumab) remain under investigation[27,84].

Vaccines

The addition of standard anticancer vaccine therapy has greatly improved long-term survival in patients with GBM. Numerous phase I to phase III trials of vaccines against glioblastoma are being conducted.

The most relevant target is epidermal growth factor receptor variant III (EGFRvIII)[15]. The EGFRvIII peptide vaccine, rindopepimut (Rintega®), was tested in phase III clinical trials, which showed its effectiveness in combination with standard chemotherapy (<https://www.clinicaltrials.gov/#NCT01480479>).

A double-blind, randomized phase III trial tested the efficacy of rindopepimut for bevacizumab-resistant patients with recurrent GBM[86].

Another peptide vaccine was studied in a phase II clinical trial, which targeted human leukocyte antigen (HLA)-restricted Wilms tumor 1 (WT1) in patients with recurrent GBM[31].

A dendritic cell vaccine (DCVax-Brain) was approved in Switzerland for the treatment of GBM. It is composed of dendritic cells with purified tumor-specific antigens or tumor cell extracts[64,65]. Experimental studies on the administration of this vaccine for newly diagnosed and recurrent GBM remain ongoing, and some of these trials have demonstrated an increase in vaccine effectiveness if boosted with the tetanus/diphtheria toxoid vaccine[51].

Another ongoing phase II clinical trial is testing the Personalized Cellular Vaccine for Recurrent Glioblastoma (PerCellVac2), which employs autologous tumor cells combined with allogeneic peripheral blood mononuclear cells as antigens (<https://www.clinicaltrials.gov/#NCT02808364>)

Heat shock proteins (HSPs) were designed as vehicles to present tumor antigens for a personalized peptide polyvalent vaccine, which was obtained by purifying HSP-96 protein complexes from patients' tumors, showing promising results in recurrent GBM[8].

1.1.1 Adoptive immunotherapies

Adoptive immunotherapies are truly a cell-based strategy and consist of engineered T cells, natural killer (NK) cells, and natural killer T (NKT) cells.

1.1.1.1 Engineered T cells

Therapeutic application of engineered T cells includes chimeric antigen receptor (CAR) T cell and the T cell receptor (TCR) transgenic T cell therapies.

Autologous or allogenic CART cells are obtained from the blood, integrated with the CAR gene by retrovirus or lentivirus vectors, induced to replicate with interleukin 2, and then transplanted. These engineered CAR T cells expose the chimeric receptor, which selectively binds molecules expressed by neoplastic cells, promoting destruction[26]. CAR genes tested for glioblastoma therapy mainly target EGFRvIII[39,58], which is a growth signal for adjacent tumor cells; human epidermal growth factor receptor 2 (HER2) [1,28]; and erythropoietin-producing hepatocellular carcinoma A2 (EphA2)[11].

TCRs are expressed on the surface of human T cells and commonly bind the major histocompatibility complex (MHC), which has an antigenic function on infected human cells and, thus, allows activation of the immune system. The TCR is composed of an alpha (α) and a beta (β) chain, which are isolated, mutated, integrated into a viral genome for replication, and inserted into patients' T cells. Therefore, TCR transgenic T cells are potentially suitable for directly activating the immune response against tumor cells.

1.1.1.1 NK cells

NK cells have a small therapeutic role in GBM because of the excessive expression of MHC class I molecules and HLA ligands on cancer cells, which bind inhibitory NK cells and killer immunoglobulin-like receptors (KIRs), negating NK cell activity[35].

Several studies have reported the use of allogenic NK cells, which cannot be recognized or inactivated by the MHC I or HLA of tumor cells, and the use of antibodies for KIRs with the aim of increasing the effect of NK cells. Another effective therapy is the use of specific NK receptors, which cause tumor cell apoptosis when activated. Navarro et al. tested the transplantation of autologous NK cells expressing KIR2DS2 receptors as potent tumor killers[24]. In addition, Yvon et al. studied the role of TGF- β in the inhibition of expression of NK activating receptors, such as

NKG2D[94]. They investigated the dominant negative TGF- β receptor II (DNRII) on cord blood NK cells and evaluated their ability to kill glioblastoma cells via retroviral transduction[94].

In addition, a new type of CAR (CAR-KHYG-1) targeting EGFRvIII and capable of inhibiting cell-growth and apoptosis has been developed.

1.1.1.1 *NKT cells*

Invariant NKT cells are characterized by the co-expression of T and NK cell markers. The activation of these cells in culture with autologous mature DCs pulsed with a synthetic glycolipid α -galactosyl ceramide can be used to enhance NKT cell cytotoxic activity against GBM[16].

Several studies have reported the role of miR-92a in the development of cancer tolerance against NKT cells via the production of an immune tolerant IL-6+ IL-10+ NKT cell phenotype and inhibition of CD8+ T cells[81].

1.1.1.1 *Hybrid NKT cell therapy*

The Autologous Lymphoid Effector Cells Specific Against Tumor cells (ALECSAT) technology was proposed by CytoVac A/S (Hørsholm, Denmark) to treat many solid tumors. This treatment takes 26 days and involves the transplantation of autologous T and NK lymphocytes, which are activated *ex vivo*. Autologous lymphocytes and monocytes are isolated from the blood, and the latter are induced to differentiate into dendritic cells (DC). DCs and lymphocytes are cultured and generate activated T helper (Th) cells, which are treated with 5-aza-2'-deoxycytidine, a DNA-demethylation agent, to express cancer/testis antigens (CTAs). The CTA-expressing activated Th cells stimulate non-activated lymphocytes, and ultimately, CD8+ cytotoxic lymphocytes (CTLs) are obtained. Cancer cells that do not express the antigen are destroyed by activated NK cells[89].

1.1 *Stem Cell-Based Therapies*

Stem cells are immature undifferentiated cells, which are found in every human tissue, with

self-renewal capacity and the ability to repair and control the tissue's functions.

In the nervous system, neural stem cells (h-NSCs) have been identified to be responsible for the regeneration and differentiation of neurons and glial cells, and they are involved in tumor responses[49,12].

In 2004, Staflin et al. reported a study on the antitumor activity of h-NSCs expressed by the intense production of TGF- β [77]. The h-NSCs can also be integrated via a viral genome, with genes codifying tumor necrosis factors or IL-12 and, due to their extreme migration capacity, can also be exploited as delivery vehicles to deliver materials to the tumor site. The extensive tumor tracking capability of NSCs and the tumoricidal potency of IL-12 are thought to render exceptional therapeutic benefits[50].

In the periphery surrounding GBM, there are glioma stem cells (GSCs), which have an enormous role in tumorigenicity and metastasis and high rates of recurrence after treatment as well as in the development of resistance to treatment.

GSCs express CD133 on their surface, and a novel therapeutic strategy is to selectively target this marker using lentiviral vectors (CD133-LV)[5].

The revolutionary technique of Cell-Systematic Evolution of Ligands by Exponential Enrichment (Cell-SELEX) leverages selective aptamers that bind to and are internalized by GSCs, leading to destruction of the GSCs[34].

Gene Therapies

Gene modification technology directly introduces genetic material carried by viral vectors into human cells, inducing *in vivo* infection. Ongoing phase I, II, and III trials employ adenoviruses, retroviruses, and lentiviruses as carriers to introduce vectors into human genes that codify therapeutic factors or enzymes.

The most useful technique exploits the insertion of the thymidine kinase (TK) gene via the herpes simplex virus (HSV) into the GBM cell genome. This action has an immediate consequence of superficial expression of HSV-TK, an optimal target for antiviral drugs (acyclovir, ganciclovir, and valacyclovir) (<https://www.clinicaltrials.gov/#NCT00002824>). The results of this

novel approach (i.e., suicide gene therapy) were shown by a randomized phase III trial with the application of adenovirus-mediated gene therapy and HSV-TK in patients with newly diagnosed glioblastoma after resection[7,30,82].

Adenovirus vectors are used to inject the p53 gene into GBM cells to replace the normal p53 pathway[40]. Another example of virotherapy is the use of poliovirus (PVSRIPO), as shown in a phase I clinical trial, which replicates and selectively destroys tumor cells and spares healthy tissue[42].

Genome Editing Therapies

This approach is based on wider DNA manipulation with the use of nucleases, which can modify and regulate genomic loci to achieve therapeutic effects. Meganucleases, zinc finger nucleases (ZFNs), and transcription activator-like effector nucleases (TALENs) are the most commonly adopted nucleases.

ZFNs and TALENs are enzymes with two domains: one destined for DNA-binding and the other for DNA-cleavage[92]. They can be delivered to tumor cells via plasmids or ex vivo, and selectively modify target genes and introduce exogenous DNA for therapeutic purposes.

One of the most advanced genome editing therapies adopted is the (CRISPR)/Cas9 system, which was originally identified in bacteria. The Cas9 nuclease protein functions as molecular scissors, cutting and altering the DNA itself, which induces specific genome changes. Cas9 programming is performed through specific guide RNAs to target specific genetic material represented by CRISPR sequences, with a much more specific and effective action than other endonucleases[19,74].

Target Therapies

The most avant-garde and revolutionary therapeutic route against malignant CNS tumors is target therapy. This therapeutic strategy focuses on GBM intrinsic targets and pathways involved in tumorigenesis and cell growth maintenance.

Tyrosine kinase (TK) inhibitors

The most involved pathway is that of TKs, which are enzymes that regulate cellular processes, proliferation, differentiation, and oncogenesis. TKs phosphorylate the tyrosine residues of some receptors and intracellular proteins, activating a cascade of second messengers involved in many cellular mechanisms.

EGFR is one of the most important targets, since it is overexpressed in 40–60% of GBMs, and the typical mutation is EGFRvIII, resulting in increased cell proliferation and invasiveness.

The available EGFR TK inhibitors are gefitinib and erlotinib, which are currently administered as monotherapy or combined with TMZ and provide minimal benefit for GBM treatment[70,37,63,68].

Platelet-derived growth factor receptors (PDGFR) are also aberrantly overexpressed and activated in GBM, stimulating tumor growth and angiogenesis. Imatinib is a TK inhibitor of the PDGFR that was tested in a phase II trial showing no significant benefits (<https://www.clinicaltrials.gov/#NCT00049127>).

Mammalian target of rapamycin (mTOR) is an intracellular protein kinase involved in cell growth signaling through the PI3K/AKT/mTOR pathway, normally implicated in the pathogenesis of high-grade gliomas. Many clinical trials on recurrent GBM tested mTOR inhibitors (sirolimus, temsirolimus, and everolimus) and a PI3K inhibitor (buparlisib) and demonstrated these agents to be inactive, with unfavorable toxicity and low tolerance in patients[68,90,88].

In addition, TK inhibitors directed against mesenchymal–epithelial transition (MET), the fibroblast growth factor receptor (FGFR), BRAF mutants (V600E), and the Ras–MAPK pathway, which are involved in glioma cell growth, spreading and apoptosis, are under consideration.

p53 Replacement

The p53/ARF/MDM2 pathway is aberrant in 84% of GBM cases. The mutation of p53 is a gain of function mutation that deregulates cell proliferation and apoptosis. A revolutionary strategy is PRIMA-1 (2, 2-bis(hydroxymethyl)-3-quinuclidinone), which is a small molecular weight compound capable of

restoring sequence-specific DNA binding to the active conformation of p53 proteins, the normal function of p53, and tumor cell apoptosis. The applicability of PRIMA-1 in clinical practice remains under investigation[85,9,62].

Discussion

GBM is the most aggressive CNS tumor and has a poor prognosis, high recurrence rate, and high mortality rate. The standard of care provides gross total surgical resection, followed by a regimen of concomitant/adjuvant TMZ combined with RT.

Surgery remains the mainstay of treatment; refinements in neurosurgical preoperative planning and intraoperative imaging, such as neuronavigation, and image-guided surgery, such as fluorescein- or 5-aminolevulinic acid (5-ALA)-based intraoperative magnetic resonance imaging (MRI), have helped to define tumor margins and maximize the extent of resection[78].

Several clinical trials demonstrated that maximum surgical resection (i.e., at least 95% of the contrast-enhancing tumor mass) improves progression-free survival at 6 months compared to subtotal resection[38,71].

In 2005, Stupp et al. designed a standard chemoradiotherapy protocol based on the results of a phase III study conducted in 85 centers with over 573 patients with GBM. They compared the results of treatment with only RT and RT plus 6 cycles of concurrent TMZ, and the 5-year survival rates were 1.9% and 9.8%, respectively. The current protocol, which was based on a revised study by Stupp et al. in 2009, includes surgery followed by RT within 6–7 weeks (total dose of 56–60 Gy in 30 fractions over 6 weeks) with concomitant TMZ at 75 mg/m² and maintenance with 6 cycles of TMZ for 28 days (150 and 200 mg/m², respectively) (15758009; 19269895).

Despite the aggressive combined approach, patients with GBM invariably relapse, with a median progression-free survival of 10 weeks and overall survival of 30 weeks.

Advances in genomic profiling, with the detection of molecular abnormalities underlying a malignant

phenotype of GBM, and the biotechnological revolution in medicine, involving neuro-oncology and other fields[69,14,22,46,48,47], have paved the way to new therapeutic prospects, personalized treatments, and novel drugs that specifically target tumor cells.

Applications of biotechnology, and specifically cell-based therapy, have allowed the use of strategies based on somatic cells, immunotherapies, staminal cells, and genome manipulation technologies.

Immunotherapies have led to an essential breakthrough in the management of high-grade gliomas. The goal of this approach is to achieve synergy between the increase in the immune response and the simultaneous inhibition of the tumor's immunosuppressive mechanisms. Checkpoint inhibitors and MAbs are mainly administered together with RT, as this combination modulates the tumor microenvironment in favor of immune stimulation and recruitment of immune cells. In addition, vaccination strategies with the choice of an appropriate target, combined with immunomodulators, is a promising lead for more durable responses in patients with GBM.

Adoptive immunotherapy is part of a broad expansion in immuno-oncology. The administered engineered T and NK cells allow bypass of antigen presentation and stimulation of a primary immune response, directly targeting specific antigens through CARs. The focal point of therapy is the development of new CARs designed to bind selective and appropriate cell surface antigens.

Among somatic cell technologies, the stem cell-based approach is also used. This approach involves autologous cells, free from immunological risk, and their intrinsic homing property makes them specific and selective for the target tissue. In addition, agents that selectively target GSCs, responsible for tumor cell renewal and recurrence after initial treatment, can theoretically revolutionize GBM management, significantly increasing progression-free and overall survival.

The main limitations of somatic cell-based therapies are the loss of their biological activity[83] and the development of adaptive solutions by the tumor through mechanisms of immune tolerance and immunophenotypic adaptations.

Gene therapy allows modification of the tumor cell genome via viral vectors. The main challenges of

this approach are the identification of target gene promoters and the choice of the most suitable viral carrier, which should have transportation, diffusion, and replication capabilities.

Lastly, the concept of target therapy dramatically changed the approach to oncological diseases, providing agents that targeted tumor-specific features, such as altered cellular signaling pathways, aberrant vascularization, and the tumor microenvironment [67,6]. In the management of malignant CNS tumors, TK inhibitors are mostly being developed to interrupt intracellular expansion and proliferation signals.

A common limitation for all these therapeutic strategies is the blood-brain barrier, which reduces the effective penetration of drugs into the tumor site. The locoregional administration of antitumor agents and innovative strategies as nanostructures employed to carry drugs can concretely improve the administration route and make the therapy more effective.

Conclusion

MAbs, primarily bevacizumab, are pivotal first-line innovative immunotherapies for high grade gliomas.

Vaccines, engineered cells, and stem cell-based and gene therapies are potential valuable options to be adopted as second-line therapies for recurrence.

Genomic profiling is essential for choosing the most suitable approach and implementing tailored and target therapy.

The effectiveness of these personalized approaches is currently being validated in ongoing clinical trials.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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