Pharmacology

Review Article

Pharmacology
DOI: 10.1159/000531319

Received: September 19, 2022
Accepted: May 5, 2023
Published online: June ▪▪▪, 2023

Glioblastoma Multiforme: The Latest Diagnostics and Treatment Techniques

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Keywords
Glioblastoma multiforme · Fluorescence diagnostics · Three-dimensional imaging · Gene mutation · Cell-free DNA · Immunotherapy · Virotherapy · Chemotherapy · Temozolomide · Larotrectinib · Tyrosine kinase inhibitors · Cancer vaccines · Oncolytic virus · Non-coding RNAs · HSV-G47Δ · Targeted therapy

Abstract

Background: Glioblastoma multiforme (GBM) is a WHO grade 4 glioma and the most common malignant primary brain tumour. Recently, there has been outstanding progress in the treatment of GBM. In addition to the newest form of GBM removal using fluorescence, three-dimensional (3D) imaging, tomoradiotherapy, moderate electro-hyperthermia, and adjuvant temozolomide (post-operative chemotherapy), new developments have been made in the fields of immunology, molecular biology, and virotherapy. An unusual and modern treatment has been created, especially for stage 4 GBM, using the latest therapeutic techniques, including immunotherapy and virotherapy. Modern oncological medicine is producing extraordinary and progressive therapeutic methods. Oncological therapy includes individual analysis of the properties of a tumour and targeted therapy using small-molecule inhibitors. Individualised medicine covers the entire patient (tumour and host) in the context of immunotherapy. An example is individualised multimodal immunotherapy (IMI), which relies on individual immunological tumour-host interactions. In addition, IMI is based on the concept of oncolytic virus-induced immunogenic tumour cell death. ***Summary:*** In this review, we outline current knowledge of the various available treatment options used in the therapy of GBM including both traditional therapeutic strategy and modern therapies, such as tomotherapy, electro-hyperthermia, and oncolytic virotherapy, which are promising treatment strategies with the potential to improve prognosis in patients with GBM. ***Key Messages:*** This newest therapy, immunotherapy combined with virotherapy (oncolytic viruses and cancer vaccines), is displaying encouraging signs for combating GBM. Additionally, the latest 3D imaging is compared to conventional two-dimensional imaging.

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Introduction

Glioblastoma multiforme (GBM) is a WHO grade 4 glioma, one of the most aggressive malignancies and also the most common malignant primary tumour of the central nervous system (CNS). GBM accounts for about half of malignant CNS tumours with a 5-year survival of 7.2% [1–3]. The incidence of GBM increases with age and is greater in men than women. Furthermore, GBM is found more often in Caucasians than in other ethnicities [4]. Tumour spreading beyond the CNS is rare. The most common sites of extra-cranial metastasis are the lungs and pleura [5, 6]. It has been established that ionising radiation and defined genetic syndromes are the only risk factors identified to date for GBM. No corroboration has been found between the risk of developing GBM and routine exposure to diagnostic radiation in either children or adults [7–9].

Standard GBM therapy includes neurosurgery, radiotherapy (tomoradiotherapy), and chemotherapy. This type of therapy has not been so successful as side effects may occur more than once, especially with chronic temozolomide (TMZ) intake; hence, there is a new form of GBM therapy which has been developed over several years. The newest scheme is immunotherapy combined with virotherapy (oncolytic viruses [OVs] and cancer vaccines [CVs]). Also, significant progress in tomo-, NanoTherm-, or immunotherapy is noticeable. The last mentioned includes checkpoint inhibitors, new antibodies, and chimeric antigen receptor T cells [10]. Personalised medicine covers the entire patient (tumour and host) in the context of immunotherapy. An example is individualised multimodal immunotherapy (IMI). This is based on individual immunological tumour-host interactions and the concept of immunogenic tumour cell death (ICD) induced by an OV [11]. Ongoing challenges to GBM treatment include insufficient resection, a high degree of heterogeneity, and an immunosuppressive microenvironment. The tumour forms a "shield" as a form of defence using both non-immune and immune mechanisms [10]. The aim of this article was to summarise the traditional and the most recently discovered GBM therapy strategies, with particular emphasis on immunological therapy, CVs, and OV.

Materials and Methods

The current state of knowledge described in this review article is based on a query of the literature available in PubMed, SINOMED, and China National Knowledge Infrastructure, conducted from January 2009 to December 2022. The following terms, along with "glioblastoma multiforme," were searched for: "fluorescence diagnostics", "three-dimensional (3D)", "gene mutation", "cell-free DNA (cfDNA)", "immunotherapy", "chemotherapy", "temozolomide", "larotrectinib", "tyrosine kinase inhibitors", "cancer vaccines", "oncolytic virus", and "targeted therapy."

Diagnosis of GBM

The standard of care for radiographic characterisation of GBM is magnetic resonance imaging, which is a widely used technique for the diagnosis and post-treatment management. The tumour size at the time of diagnosis is usually around 4 cm [12, 13]. A definitive diagnosis is based on histopathological inspections of the intraoperatively removed tumour or its parts, using traditional histological, cytologic, and histochemical methods. When neurosurgical lesion resection is impossible, a fine-needle aspiration biopsy is carried out [3, 12, 14].

Glial fibrillary acidic protein (GFAP) is a part of the cytoskeletal protein family and is widely expressed in astroglial cells as well as in GBM cells. The loss of GFAP expression indicates significantly undifferentiated tumour cells but does not determine tumour progression and development. It may be concluded that serum GFAP constitutes a diagnostic biomarker for GBM [15, 16].

Traditional GBM Therapy

Surgical Treatment

The term "neurosurgery" was first used in English in 1904 [17], but the first glioma resection was performed in 1884 by Rickman Godlee [18]. The aim of neurosurgical therapy is the gross total resection of the tumour mass, which is not always successful, especially in GBMs that do not have a clear margin [19–21]. Oncological fluorescence is used in the surgical removal of GBM. Launching this method of intraoperative diagnostics, after implementing neuromonitoring, intraoperative awakening, or tractography methods, is another step towards further increasing the effectiveness and safety of these operations. Before surgery (about 24 h), the patient receives oral oncological fluorescence (5-aminolevulinic acid [5-ALA]), which uses the unique phenomenon that the tumour cells in the brain tumour (GBM) accumulate contrast. As a precursor to haemoglobin synthesis, 5-ALA leads to the accumulation of fluorescent porphyrins [22], and oral administration of 5-ALA leads to the accumulation of protoporphyrin IX in the GBM. To sum up,

during the procedure, after illuminating the surgical field with light of a specific colour (usually pink/red), the areas covered by the neoplastic infiltrate automatically start to glow. The more intense the staining, the more the observed area has been infiltrated by the tumour [23–25]. This type of therapy (using 5-ALA) is very popular in Europe but has not been approved in the USA [23].

TMZ as Chemotherapy

TMZ (a DNA alkylating, nitrogen mustard derivative, dacarbazine, C6H6N6O2) was introduced in 1999 (the first licence was obtained then) for the most malignant grade [26] of GBM. TMZ (4-methyl-5-oxo-2,3,4,6,8-pentazabicyclo [4.3.0] nona-2,7,9-triene-9-carboxamide) is a first-line chemotherapy drug approved for the treatment of GBM by the Food and Drug Administration (FDA) [27] and Occupational Exposure to Hazardous Drugs (OSHA) [28]. Currently, the standard of care after surgical resection is radiotherapy (preferably image-guided intensity modulated radiation therapy [IG-IMRT] tomotherapy) with adjuvant TMZ [29], that is, combination therapy followed by monotherapy. In combination therapy (tomotherapy and chemotherapy), TMZ is administered orally, usually at a dose of 75 mg/m^2 of body surface area per day for 42 days (up to 49 days) along with targeted tomotherapy (60 Gy given in 30 doses). In the absence of complications, TMZ monotherapy is then administered after 4 weeks of combined therapy [30, 31]. It should be emphasised, however, that chemotherapy is toxic to proliferating cells, which is a beneficial effect, but by damaging healthy cells, it can cause many complications, for example, thrombocytopaenia and neutropaenia, cytomegalovirus or hepatitis B virus, fatal liver failure, *Pneumocystis jirovecii*, or Stevens-Johnson syndrome [32, 33].

Currently, medical tests are being carried out using TMZ nano or nanomedicine. In this new type of therapy – "promises made by the nanocarriers in glioblastoma therapy" – polymer nanoparticles have a polymer coating to protect the drug from early degradation. As a result, TMZ nano is released continuously. The drug can also target the action of surface modification (attachment of specific ligands, peptides, antibodies, etc.) [34].

Pembrolizumab – Humanised Monoclonal Antibody

In addition to TMZ, pembrolizumab has been recently used in the treatment of GBM (grade 4). The goal of this therapy is to restore the activity of T lymphocytes (using the patient's own immune system). Pembrolizumab blocks the programmed cell death receptor on the lymphocyte surface. In other words, this drug prevents the GBM from neutralising the lymphocytes by blocking the connection between the PD-L1 protein of GBM and the programmed cell death receptor. This drug is administered to patients diagnosed with GBM not only in the post-operative period but also before planned surgical treatment. Common adverse events associated with pembrolizumab use may include fatigue, diarrhoea, thyroid disorders, rash, and pruritus [35–37].

A Revolution in Targeted (Individual) Therapy

The main current trends involve the study of mutations and tumour heterogeneity, which are essential in individual therapy. In patients with GBM, so-called cell-free DNA (cfDNA) was identified, which was extracted from plasma and fresh tumour samples. This study was conducted by Palande et al. [38] in a group of 180 patients, where significantly elevated cfDNA was found, compared to patients in the control group. In addition, these scientists detected "unique mutations" when studying cfDNA along with tumour DNA, which were consistent with the COSMIC database (TP53, 18.75%; epidermal growth factor receptor (EGFR), 37.5%; NF1, 12.5%; LRP1B, 25%; IRS4, 25%). Additionally, these scientists identified gene-to-gene fusions in cfDNA and tumour DNA as PDGFRA mutations. They also proved that PDGFRA fusion proteins play the main role in initiating therapy with protein kinase inhibitors (imatinib, sunitinib, and sorafenib). Interestingly, in their further studies, these researchers identified numerous genes (BCR-ABL1, COL1A1-PDGFB, NIN-PDGFRB in 8% of patients, and FGFR1-BCR in 4% of patients) in the patients' cfDNA that could indicate the use of imatinib analogues. The use of other medications (such as crizotinib, entrectinib, or larotrectinib) is possible thanks to the ROS1 fusion (CEP85L-ROS1 and GOPC-ROS1), which has been demonstrated in the cfDNA of 8% of patients. These studies have additionally proven the amazing benefits of targeted therapy.

Tyrosine Kinase Inhibitors (Imatinib, Sunitinib, and Sorafenib)

Protein kinases are enzymes that phosphorylate (phosphorylation is a chemical reaction involving the attachment of a phosphate group) other proteins in the cell and thus regulate their activity. In normal cells, the activity of protein kinases is strictly regulated, but in cancer cells, it is often out of control and excessive. This causes disturbances in the functioning of many cellular pathways and the control of the cell cycle, consequently leading to the stimulation of cell division and uncontrolled tumour

growth. Inhibition of the excessive activity of protein kinases is the therapeutic goal of this group of anti-cancer drugs [39–44].

1. Imatinib is an organic chemical compound used as a drug in the form of a salt (metal sulfonate) in the treatment of many other cancers. Imatinib mesylate is metabolised mainly to the N-desmethyl derivative of piperazine with similar potency. The cytochrome P450 isoenzyme CYP3A4 participates in the biotransformation of imatinib. Imatinib competitively inhibits the CYP2C9, CYP2D6, and CYP3A4/5 isozymes. This drug is the first inhibitor that inhibits tyrosine kinase receptors [40].
2. Sunitinib inhibits multiple receptor tyrosine kinases that are involved in tumour growth, neoangiogenesis, and metastatic disease dissemination. Sunitinib has been identified as an inhibitor of platelet growth factor receptors, vascular endothelial growth factor receptors (VEGFR1, VEGFR2, and VEGFR3), stem cell factor receptors (KIT), FMS-like tyrosine kinase-3 (FLT3), colony-stimulating factor 1 receptors (CSF-1R), and glial-derived neurotrophic factor receptors (RET). In biochemical and cell tests, the basic metabolite of sunitinib exhibits sunitinib-like activity [41].
3. Sorafenib is a multi-kinase inhibitor. This drug inhibits the Raf kinase and thus blocks the Raf signalling cascade. Additionally, cell division and proliferation are reduced. It also inhibits several tyrosine kinases, including those of the VEGF signalling pathway. Signalling cascades are blocked, and tumour angiogenesis is reduced [42, 43].

Other Medications

Other medications include crizotinib, entrectinib, and larotrectinib. Recent research by König et al. [44] has shown a remarkable response to the treatment of GBM with larotrectinib. This case allows regular testing of NTRK fusion proteins. This drug inhibits tropomyosin kinase receptors TrkA, TrkB, and TrkC. Larotrectinib is the first (specially developed) drug in its class to be used to treat any cancer containing certain mutations [44, 45]. Several earlier drugs, including pembrolizumab, have been eventually approved by the FDA to treat cancer-specific mutations, but these drugs were initially developed for particular cancer types [36, 37].

Modern GBM Therapies

Tomoradiotherapy instead of Classic Radiotherapy

Until recently, classical radiotherapy was used [46, 47]. Currently, tomotherapy is used, that is, a technologically advanced accelerator for irradiation using the IG-IMRT method. This method enables the delivery of a specific and planned dose of radiation to the neoplastic tumour, sparing healthy tissue. IG-IMRT additionally enables the treatment to be adapted, that is, changing the treatment plan depending on changing conditions (tissue swelling, tumour volume reduction, patient weight loss) [48].

Modern 3D Imaging Compared to Conventional Two-Dimensional Imaging and Proton Therapy

GBM is a malignancy with an exceptionally poor prognosis. It is not always possible to determine how this tumour will respond to various types of therapy. Moreover, so far, there is no precise information about the effect of protons on GBM at the cellular level [49]. Conventional X-ray radiation therapy is known to damage both neoplastic cells and the surrounding healthy brain tissue. Proton beam therapy is a newer technique to combat GBM that improves on the shortcomings of conventional radiation therapy. This therapy uses protons instead of X-rays. Compared to X-rays, protons theoretically focus only on neoplastic tissue, and damage to healthy tissue is rare [50]. Unfortunately, due to the high cost of proton radiotherapy, there is no clinical information on the effectiveness of GBM proton irradiation, particularly at the cellular level [49, 50]. Akolawala et al. [51] have recently shown the current effectiveness of medications and radiation. These scientists used the latest 3D imaging, comparing it to typical 2D imaging. In their study, a 3D "engineering scaffold" was designed depending on the so-called blood vessel geometry. These vessels play an essential role in the mechanisms of colonising GBM cells. Gamma H2A.X was used as a fluorescent biomarker to detect DNA damage caused by proton beams in neoplastic cells. In this study, the superiority of 3D (engineered cellular microenvironments) over 2D (monolayer cell culture) has been proven, providing a better in vivo model.

Modulated Electro-Hyperthermia

Hyperthermia therapy can lead to intra-/extracellular heat-regulated modifications that may promote cell necrosis and/or apoptosis. What is more, hyperthermia therapy can improve the effect of chemotherapy through enhanced substrate delivery, and it also increases the sensitivity of malignant cells to chemo- and radiation therapy [52, 53].

Fiorentini and Szasz [54] worked out the biophysics of modulated electro-hyperthermia (mEHT) in detail. mEHT aims to combine heat with the action of electric fields to completely damage the tumour (cancerous

tissue). The differences (electrical properties) between diseased (cancerous) and healthy tissue should be taken into account [54–58]. According to conventional hyperthermia, the dose is measured by the temperature reached in 90% of the tumour. This requires monitoring with intra-tumour thermometers or MR [59] technology. Scientific research by Fiorentini and Szasz [54] has shown that doses of mEHT are not measured by the temperature in the tumour, but rather by the amount of energy that needs to be deposited in the tumour to produce sensitising and cell-killing effects.

NanoTherm Therapy: A Promising Method of Treating Recurrent GBM

NanoTherm® therapy is a method used in patients with GBM when classical methods of treatment have been exhausted. This innovation is based on the combination of thermal ablation and nanotechnology. A specially developed and patented ferrofluid, containing magnetic nanoparticles (1.7×10^{17}/mL) of iron oxide with a size of about 15 nm each, is introduced directly into the tumour or the wall of the cavity created after tumour resection. These nanoparticles are surrounded by a special coating and attack the neoplastic tissue, sparing the adjacent healthy tissue. However, before they attack the neoplastic tissue, they are subjected to an alternating magnetic field, which is produced by a special generator – NanoActivator®. This magnetic field has a fast-changing effect, and the temperature of the nanoparticles increases, destroying neoplastic cells [60].

IMI Based on CVs and OVs

Effective immunotherapy can be achieved through two strategic approaches: (1) CVs and (2) virotherapy. In the emerging field of immuno-oncology, CVs and OVs are promising treatments. The anti-cancer effect of this type of immunotherapy contains initiating a new immune response or strengthening the existing immune response against cancer cells [10].

Cancer Vaccines

CVs are anti-cancer vaccines used in cancer patients for active specific immunisation. The resulting immunisation causes T cells to respond to the tumour. The following lymphocytes are distinguished among T cells: (1) CD4 + T lymphocytes with Th1 polarisation; (2) cytotoxic CD8 + T cells with T1 polarisation (CTL); and (3) tumour antigen (TA)-reactive memory T lymphocytes (MTC) [1]. CVs activate a specific immunisation that tells the patient's immune system about tumour-associated antigens [61]. TA-presenting vaccines can be based on peptides, DNA, and dendritic cells (DCs), as antigen presenting cells (APCs) [10, 11]. It should be emphasised that, for example, DC cells (professional APCs) as CVs may be loaded with specific peptides [62–65], autologous tumour lysate [11, 66], nucleotides (DNA [67] or RNA [68]) obtained from a tumour or, for example, from viruses [69].

Virotherapy

OVs, by replicating selectively, play an indispensable role – they "kill" tumour cells, not through direct viral oncolysis but through ICD inducers. The ICD enables the recruitment of APCs, which results in the promotion of APC maturation, and there is also an interaction between APCs and dying cells. ICD promotes the phagocytosis of dying cells and the maturation of APCs. Moreover, ICD leads to the migration of APCs and the related interaction with T cells (cross-priming) [10]. However, the blood-brain barrier may limit the delivery of viral vectors, considerably compromising their oncolytic efficacy [70]. Another pitfall may be resistance to virotherapy generated by glioma stem cells and glioma-associated mesenchymal stem cells [71, 72].

The Immune-Oncological Centre Cologne (IOZK) in Germany (Köln) has developed IMI [11, 63, 67], which aims to stimulate the strong specific immune responses mediated by T lymphocytes against tumour-associated antigens in cancer patients (with unique neoplastic neo-antigens) [73]. These scientists developed an anti-cancer vaccine called IO-VACR, which is produced individually for each patient. In addition to DCs, IO-VACR also contains avian OV, or Newcastle disease virus (NDV), which enhances the immunogenicity of the vaccine. The virus was first produced by IOZK in 2015 [74].

The Role of Small Non-Coding RNAs in HSV-G47Δ OV Infection Therapy in Stem Cells in GBM

Cancer cells called glioblastoma cancer stem cells (GBM-CSCs) have been proven to be inherently quite resistant to chemo-radiotherapy, chemotherapy (e.g., TMZ), and radiotherapy, which causes frequent recurrences of this very malignant disease [75–77]. It should be emphasised that GBM is a very invasive tumour [78, 79] containing very aggressive self-renewing cells. These neoplastic cells (GBM-CSCs) are characterised by a very strong carcinogenicity [80] and, therefore, the importance of this viral therapy should be emphasised. Experimental studies have shown that hypoxia increases the aggressiveness of cancer cells, which leads to the induction of angiogenesis, autophagy, and the inhibition of apoptosis [81–84].

Recent research by Vazifehmand et al. [85] has shown the important role of small non-coding RNAs, which consist of microRNAs (miRNAs; 17–22 nucleotides) and

long non-coding RNAs (lncRNAs; ˃ 200 nucleotides). Lee and Dutt [86] have shown that non-coding RNAs play an important role in various GBM processes, such as tumour initiation, apoptosis, proliferation, and angiogenesis. The same scientists were the first to show resistance to chemotherapy (e.g., TMZ) and radiotherapy. It should be added that Vazifehmand et al. [85] have shown that non-coding RNAs, that is, miRNA and lncRNA, are the main target for the oncological virus (HSV-G47Δ) affecting GBM-CSC in both microenvironments (hypoxic and normoxic conditions). miRNAs are short, single-stranded RNAs that regulate gene expression during the post-transcriptional process [86, 87]. lncRNAs are non-coding proteins performing their biological function at the transcriptional, post-transcriptional, and epigenetic levels [88]. Dysregulation of specific lncRNAs plays a major role in the progression of glioblastoma, intensifying its malignancy [89]. Recent research by Vazifehmand et al. [85] has shown that non-coding RNAs (miRNA and lncRNA) are nothing more than a potential target for the HSV-G47Δ OV in the microenvironments of hypoxia and normoxia. Their research has revealed that lncRNA can be targeted by HSV-G47Δ (in GBM-CSC) in these two microenvironments (normoxia and hypoxia).

Targeting non-coding RNAs in GBM therapy is a very serious and promising strategy. Until recently, despite various types of multimodal targeted therapies, GBM has been considered a deadly disease with limited treatment efficacy. On the other hand, the studies show that a therapy including non-coding RNAs and the IOZK vaccines presented above (these vaccines have been used for many years) will be effective in the future [11].

Selective Sodium Iodide Symporter Gene Therapy

The sodium iodide symporter (NIS) gene is a promising, efficient, and safe therapy gene for systemic administration. The application of 131-I or 188Re and their NIS-mediated collection in the tumour environment allow therapeutic cytoreduction through the β emission of these radionuclides. This therapeutic concept is established, safe, and used for the treatment of thyroid cancer [90, 91]. In a preclinical study into prostate cancer, Spitzweg et al. [92] took the first step towards human NIS gene transfer in non-thyroidal cancer. Spellerberg et al. [93] used EGFR-targeted polyplexes (GE11). Due to EGFR overexpression in GBM cells, EGFR is an attractive candidate for GBM-targeting therapy. Mice bearing an orthotopic glioblastoma were treated with mono-dibenzocyclooctyne (DBCO)-PEG24-GE11/NIS or bisDBCO-PEG24-GE11/NIS, and then 124I uptake was estimated by positron emission tomography imaging. In the therapy group, a considerable decrease in tumour growth and an extension of survival were observed. Further investigations may reveal the use of radioisotope 131-I in effective therapy for GBM.

Summary

Currently, neurosurgical treatment is still the standard for the treatment of GBM with adjuvant therapy in the form of radio- and chemotherapy. The use of 5-ALA increases the effectiveness of neurosurgical intervention as it allows healthy tissues to be distinguished from the remaining small fragments of the tumour, which in normal daylight are indistinguishable from healthy tissue. The scope of resection is therefore more complete. At the same time, even though, as a result of the operation, a larger area of the pathological lesion is excised, this surgical method is less risky for the patient [23–25].

After tumour removal, tomoradiotherapy is now used instead of classic radiotherapy, which contributes to better protection of healthy tissues. At the same time, adjuvant TMZ is used. The use of TMZ nano, or nanomedicine, is being tested as a new type of therapy. Unfortunately, due to the infiltrating nature of tumour growth and its location, there are times when it is not possible to perform surgery on a tumour. As a result, IMI comes to the fore. This is based on the individuality of immunological tumour-host interactions and the concept of ICD induced by an OV [10]. The same author in another publication has shown that PAMP, DAMP, and the endoplasmic reticulum play an important role in OV-induced ICD. As previously mentioned, an example of an OV would be an attenuated avian RNA virus, or oncological NDV, which is an essential, life-saving virus [94].

OVs refer to non-pathogenic viruses that specifically infect cancer cells and cause oncolysis, thereby initiating post-oncolytic anti-tumour immunity. Like other agents (e.g., some cytostatic, ionising radiation), OVs can be classified as ICD inducers. OVs are viruses that can replicate in neoplastic cells at the same time as lysing them, that is, breaking them down. Galluzzi et al. [95] show that ICD causes immunogenic apoptosis, necrosis/necroptosis, proptosis, and autophagic (cancerous) cell death. In summary, ICD facilitates APC recruitment, directs the interaction between APCs and dying cells, promotes the phagocytosis of dying cells, and promotes APC maturation, migration, and the related interaction with T cells (cross-priming).

Treatment with OVs turns out to be much more beneficial and safer, with few side effects. It seems,

however, that OVs "have problems" with infecting cancer cells. Why? Well, before the OV reaches the infected cell, natural mechanisms get in the way to prevent it from spreading throughout the body. But in such a situation it has additionally been proven that oncolytic NDV can overcome resistance to treatment [66, 94]. It has additionally been proven that small non-coding RNAs, that is, miRNA and lncRNA, are the main targets for the HSV-G47Δ OV in both microenvironments, and this is a very promising approach to GBM therapy [85].

This is how the immune system works; after recognising a virus, it defends itself and tries to destroy the intruder. This means that OVs must reach the infected cell before they can be recognised and destroyed by the immune system. Despite these difficulties, scientists are still conducting research on other cancers, including melanoma, pancreatic cancer, and breast cancer. Therefore, the current trends in GBM therapy involve primarily the study of mutations and tumour heterogeneity, which are essential in individual therapy.

Conclusion

At present, due to new advances in medicine, including virology, molecular biology, and immunology therapy, there must be a transformation in clinical trials, requiring changes in both the approach to clinical trials and the individual approach to the patient. This paper is a summary of the current therapy strategies for GBM, for which there were previously only a few therapeutic options. Cross-sectional knowledge about modern methods of treatment can be an important guide in treatment selection, with particular emphasis on its individualisation.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

This study received no funding.

Author Contributions

M.B., K.D., N.S.-G., J.M., J.K., P.G., T.H., A.M.L., and R.CZ. performed the literature research and drafted the manuscript. A.Cz., S.V.G., and M.R. coordinated the work and wrote the final manuscript. All authors discussed and corrected the final version of the manuscript.

References

1 Koshy M, Villano JL, Dolecek TA, Howard A, Mahmood U, Chmura SJ, et al. Improved survival time trends for glioblastoma using the SEER 17 population-based registries. J Neuro Oncol. 2012;107(1):207–12.
2 Ostrom QT, Patil N, Cioffi G, Waite K, Kruchko C, Barnholtz-Sloan JS. CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2013–2017. Neuro Oncol. 2020;22(12 Suppl 2):iv1–iv96.
3 Wu W, Klockow JL, Zhang M, Lafortune F, Chang E, Jin L, et al. Glioblastoma multiforme (GBM): an overview of current therapies and mechanisms of resistance. Pharmacol Res. 2021;171:105780.
4 Davis ME. Glioblastoma: overview of disease and treatment. Clin J Oncol Nurs. 2016;20(5 Suppl l):S2–8.
5 Luan XZ, Wang HR, Xiang W, Li SJ, He H, Chen LG, et al. Extracranial multiorgan metastasis from primary glioblastoma: a case report. World J Clin Cases. 2021;9(33):10300–7.
6 Hata N, Katsuta T, Inoue T, Arikawa K, Yano T, Takeshita M, et al. Extracranial metastasis of glioblastoma to the lung and heart with a histological resemblance to small cell carcinoma of the lung: an autopsy case. Noshinkeigeka. 2001;29(5):433–8.
7 Hanif F, Muzaffar K, Perveen K, Malhi SM, Simjee SU. Glioblastoma multiforme: a review of its epidemiology and pathogenesis through clinical presentation and treatment. Asian Pac J Cancer Prev. 2017;18(1):3–9.
8 Braganza MZ, Kitahara CM, Berrington de Gonzalez A, Inskip PD, Johnson KJ, Rajaraman P. Ionizing radiation and the risk of brain and central nervous system tumors: a systematic review. Neuro Oncol. 2012;14(11):1316–24.
9 Prasad G, Haas-Kogan DA. Radiation-induced gliomas. Expert Rev Neurother. 2009;9(10):1511–7.
10 Schirrmacher V. Cancer vaccines and oncolytic viruses exert profoundly lower side effects in cancer patients than other systemic therapies: a comparative analysis. Biomedicines. 2020;8(3):61.
11 Schirrmacher V, Lorenzen D, Van Gool SW, Stuecker W. A new strategy of cancer immunotherapy combining hyperthermia/oncolytic virus pretreatment with specific autologous anti-tumor vaccination-a review. Austin Oncol Case Rep. 2017;2:1006.
12 Ulutin C, Fayda M, Aksu G, Cetinayak O, Kuzhan O, Ors F, et al. Primary glioblastoma multiforme in younger patients: a single-institution experience. Tumori. 2006;92(5):407–11.
13 Shukla G, Alexander GS, Bakas S, Nikam R, Talekar K, Palmer JD, et al. Advanced magnetic resonance imaging in glioblastoma: a review. Chin Clin Oncol. 2017;6(4):40.
14 Katsetos CD, Dráberová E, Legido A, Dumontet C, Dráber P. Tubulin targets in the pathobiology and therapy of glioblastoma multiforme. I. Class III beta-tubulin. J Cel Physiol. 2009;221(3):505–13.
15 Wilhelmsson U, Eliasson C, Bjerkvig R, Pekny M. Loss of GFAP expression in high-grade astrocytomas does not contribute to tumor development or progression. Oncogene. 2003;22:3407–11.

16 Jung CS, Foerch C, Schänzer A, Heck A, Plate KH, Seifert V, et al. Serum GFAP is a diagnostic marker for glioblastoma multiforme. Brain. 2007;130(Pt 12):3336–41.
17 Lichterman B. Emergence and early development of Russian neurosurgery (1890s-1930s). J Hist Neurosci. 2007;16(1–2):123–37.
18 Kirkpatrick DB. The first primary brain-tumor operation. J Neurosurg. 1984;61(5):809–13.
19 Lacroix M, Abi-Said D, Fourney DR, Gokaslan ZL, Shi W, DeMonte F, et al. A multivariate analysis of 416 patients with glioblastoma multiforme: prognosis, extent of resection, and survival. J Neurosurg. 2001;95(2):190–8.
20 Hefti M, von Campe G, Moschopulos M, Siegner A, Looser HH, Landolt H. 5-aminolevulinic acid induced protoporphyrin IX fluorescence in high-grade glioma surgery: a one-year experience at a single institutuion. Swiss Med Wkly. 2008;138(11–12):180–5.
21 McGirt MJ, Chaichana KL, Gathinji M, Attenello FJ, Than K, Olivi A, et al. Independent association of extent of resection with survival in patients with malignant brain astrocytoma. J Neurosurg. 2009;110(1):156–62.
22 Regula J, MacRobert AJ, Gorchein A, Buonaccorsi GA, Thorpe SM, Spencer GM, et al. Photosensitisation and photodynamic therapy of oesophageal, duodenal, and colorectal tumours using 5 aminolaevulinic acid induced protoporphyrin IX--a pilot study. Gut. 1995;36(1):67–75.
23 Roberts DW, Valdes PA, Harris BT, Hartov A, Fan X, Ji S, et al. Glioblastoma multiforme treatment with clinical trials for surgical resection (aminolevulinic Acid). Neurosurg Clin N Am. 2012;23(3):371–7.
24 Stummer W, Stepp H, Möller G, Ehrhardt A, Leonhard M, Reulen HJ. Technical principles for protoporphyrin-IX-fluorescence guided microsurgical resection of malignant glioma tissue. Acta Neurochir. 1998;140(10):995–1000.
25 Duffner F, Ritz R, Freudenstein D, Weller M, Dietz K, Wessels JT. Specific intensity imaging for glioblastoma and neural cell cultures with 5-aminolevulinic acid-derived protoporphyrin IX. J Neuro Oncol. 2005;71(2):107–11.
26 Alifieris C, Trafalis DT. Glioblastoma multiforme: pathogenesis and treatment. Pharmacol Ther. 2015;152:63–82.
27 FDA Datenblatt Temodar (PDF) Letzte Revision 2011. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/.
28 OSHA Technical Manual, TED 1-0.15A, Section VI: [Chapter 2]. Controlling Occupational Exposure to Hazardous Drugs 1999. Available from: https://www.osha.gov/enforcement/directives/ted-01-00-015-5.
29 Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med. 2005;352(10):987–96.
30 Ljubimova JY, Sun T, Mashouf L, Ljubimov AV, Israel LL, Ljubimov VA, et al. Covalent nano delivery systems for selective imaging and treatment of brain tumors. Adv Drug Deliv Rev. 2017;113:177–200.
31 Mutter N, Stupp R. Temozolomide: a milestone in neuro-oncology and beyond? Expert Rev Anticancer Ther. 2006;6(8):1187–204.
32 Temodar (temozolomide) label. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021029s031lbl.pdf.
33 Scaringi C, De Sanctis V, Minniti G, Enrici RM. Temozolomide-related hematologic toxicity. Onkologie. 2013;36(7–8):444–9.
34 Dyrka K, Czarnywojtek A, Borowska M, Kościński J, Moskal J, Sawicka-Gutaj N, et al. Temozolomide: a cytostatic drug that is still important today. Acta Pol Pharm. 2023;79(6):763–75.
35 Radiation therapy with temozolomide and pembrolizumab in treating patients with newly diagnosed glioblastoma. Available from: https://clinicaltrials.gov/ct2/show/NCT02530502.
36 Baxi S, Yang A, Gennarelli RL, Khan N, Wang Z, Boyce L, et al. Immune-related adverse events for anti-PD-1 and anti-PD-L1 drugs: systematic review and meta-analysis. BMJ. 2018;360:k793.
37 Reardon DA, Kim TM, Frenel JS, Santoro A, Lopez J, Subramaniam DS, et al. Results of the phase 1B KEYNOTE-028 multi-cohort trial of pembrolizumab monotherapy in patients with recurrent PD-L1-positive glioblastoma multiforme (GBM). Neuro Oncol. 2016;18(Suppl l_6):25–6.
38 Palande V, Siegal T, Detroja R, Gorohovski A, Glass R, Flueh C, et al. Detection of gene mutations and gene-gene fusions in circulating cell-free DNA of glioblastoma patients: an avenue for clinically relevant diagnostic analysis. Mol Oncol. 2022;16(10):2098–114.
39 Aurisicchio L, Pallocca M, Ciliberto G, Palombo F. The perfect personalized cancer therapy: cancer vaccines against neoantigens. J Exp Clin Cancer Res. 2018;37(1):86.
40 [Gleevec (imatinib mesylate) tablet. Daily Med; U.S. National Library of Medicine].
41 Sun L, Liang C, Shirazian S, Zhou Y, Miller T, Cui J, et al. Discovery of 5-[5-fluoro-2-oxo-1,2-dihydroindol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylaminoethyl)amide, a novel tyrosine kinase inhibitor targeting vascular endothelial and platelet-derived growth factor receptor tyrosine kinase. J Med Chem. 2003;46(7):1116–9.
42 Strumberg D. Preclinical and clinical development of the oral multikinase inhibitor sorafenib in cancer treatment. Drugs Today. 2005;41(12):773–84.
43 Murphy DA, Makonnen S, Lassoued W, Feldman MD, Carter C, Lee WM. Inhibition of tumor endothelial ERK activation, angiogenesis, and tumor growth by sorafenib (BAY43-9006). Am J Pathol. 2006;169(5):1875–85.
44 König D, Hench J, Frank S, Dima L, Bratic Hench I, Läubli H. Larotrectinib response in NTRK3 fusion-driven diffuse high-grade glioma. Pharmacology. 2022;107(7–8):433–8.
45 Subbiah V, Velcheti V, Tuch BB, Ebata K, Busaidy NL, Cabanillas ME, et al. Selective RET kinase inhibition for patients with RET-altered cancers. Ann Oncol. 2018;29(8):1869–76.
46 Parvez K, Parvez A, Zadeh G. The diagnosis and treatment of pseudoprogression, radiation necrosis and brain tumor recurrence. Int J Mol Sci. 2014;15(7):11832–46.
47 Ellingson BM, Chung C, Pope WB, Boxerman JL, Kaufmann TJ. Pseudoprogression, radionecrosis, inflammation or true tumor progression? Challenges associated with glioblastoma response assessment in an evolving therapeutic landscape. J Neuro Oncol. 2017;134(3):495–504.
48 Fraass BA, Kessler ML, McShan DL, Marsh LH, Watson BA, Dusseau WJ, et al. Optimization and clinical use of multisegment intensity-modulated radiation therapy for high-dose conformal therapy. Semin Radiat Oncol. 1999;9(1):60–77.
49 Vogelius IR, Bentzen SM. Proton vs photon radiation therapy for glioblastoma: maximizing information from trial. Neuro Oncol. 2022;24(5):849–50.
50 Chung C, Brown PD, Wefel JS. Lessons learned from proton vs photon radiation therapy for glioblastoma signal-finding trial. Neuro Oncol. 2022;24(5):851.
51 Akolawala Q, Rovituso M, Versteeg HH, Rondon AMR, Accardo A. Evaluation of proton-induced DNA damage in 3D-engineered glioblastoma microenvironments. ACS Appl Mater Inter. 2022;14(18):20778–89.
52 Chu KF, Dupuy DE. Thermal ablation of tumours: biological mechanisms and advances in therapy. Nat Rev Cancer. 2014;14(3):199–208.
53 Skandalakis GP, Rivera DR, Rizea CD, Bouras A, Jesu Raj JG, Bozec D, et al. Hyperthermia treatment advances for brain tumors. Int J Hyperthermia. 2020;37(2):3–19.
54 Fiorentini G, Szasz A. Hyperthermia today: electric energy, a new opportunity in cancer treatment. J Cancer Res Ther. 2006;2:41–6.
55 Szigeti GP, Szasz O, Hegyi G. Personalised dosing of hyperthermia. J Cancer Diagn. 2016;01(02):1–9.
56 Szasz O, Szigeti G, Szasz A. Connections between the specific absorption rate and the local temperature. Open J Biophys. 2016;06(03):53–74.
57 Vincze G, Szasz O, Szasz A. Generalization of the thermal dose of hyperthermia in oncology. Open J Biophys. 2015;05(04):97–114.
58 Andocs G, Szasz O, Szasz A. Oncothermia treatment of cancer: from the laboratory to clinic. Electromagn Biol Med. 2009;28(2):148–65.

59 Van Rhoon GC. Is CEM43 still a relevant thermal dose parameter for hyperthermia treatment monitoring? Int J Hyperth. 2016;32(1):50–62.
60 https://www.magforce.com/news/?article=375.
61 Lowenfeld L, Mick R, Datta J, Xu S, Fitzpatrick E, Fisher CS, et al. Dendritic cell vaccination enhances immune responses and induces regression of HER2 pos DCIS independent of route: results of randomized selection design trial. Clin Cancer Res. 2017;23(12):2961–71.
62 Obara W, Kanehira M, Katagiri T, Kato R, Kato YR, Takata R. Present status and future perspective of peptide-based vaccine therapy for urological cancer. Cancer Sci. 2018;109(3):550–9.
63 Chamani R, Ranji P, Hadji M, Nahvijou A, Esmati E, Alizadeh AM. Application of E75 peptide vaccine in breast cancer patients: a systematic review and Meta-analysis. Eur J Pharmacol. 2018;831:87–93.
64 Hilf N, Kuttruff-Coqui S, Frenzel K, Bukur V, Stevanović S, Gouttefangeas C, et al. Actively personalized vaccination trial for newly diagnosed glioblastoma. Nature. 2019;565(7738):240–5.
65 Schirrmacher V, van Gool S, Stuecker W. Breaking therapy resistance: an update on oncolytic Newcastle disease virus for improvements of cancer therapy. Biomedicines. 2019;7(3):66.
66 Artusio E, Hathaway B, Stanson J, Whiteside TL. Transfection of human monocyte-derived dendritic cells with native tumor DNA induces antigen-specific T-cell responses in vitro. Cancer Biol Ther. 2006;5(12):1624–31.
67 Anguille S, Van de Velde AL, Smits EL, Van Tendeloo VF, Juliusson G, Cools N, et al. Dendritic cell vaccination as postremission treatment to prevent or delay relapse in acute myeloid leukemia. Blood. 2017;130(15):1713–21.
68 Wang B, He J, Liu C, Chang L. An effective cancer vaccine modality: lentiviral modification of dendritic cells expressing multiple cancer-specific antigens. Vaccine. 2006;24(17):3477–89.
69 Van Gool SW, Makalowski J, Feyen O, Prix L, Schirrmacher V, Stuecker W. The induction of immunogenic cell death (ICD) during maintenance chemotherapy and subsequent multimodal immunotherapy for glioblastoma (GBM). Austin Oncol Case Rep. 2018;3:1010.
70 Martikainen M, Essand M. Virus-based immunotherapy of glioblastoma. Cancers (Basel). 2019;11(2):186.
71 Zhang Q, Liu F. Advances and potential pitfalls of oncolytic viruses expressing immunomodulatory transgene therapy for malignant gliomas. Cell Death Dis. 2020;11(6):485.
72 Audia A, Conroy S, Glass R, Bhat KPL. The impact of the tumor microenvironment on the properties of glioma stem-like cells. Front Oncol. 2017;7:143.
73 Gubin MM, Artyomov MN, Mardis ER, Schreiber RD. Tumor neoantigens: building a framework for personalized cancer immunotherapy. J Clin Invest. 2015;125(9):3413–21.
74 Schirrmacher V. Oncolytic newcastle disease virus as a prospective anti-cancer therapy. A biologic agent with potential to break therapy resistance. Expert Opin Biol Ther. 2015;15(12):1757–71.
75 Beier D, Schriefer B, Brawanski K, Hau P, Weis J, Schulz JB, et al. Efficacy of clinically relevant temozolomide dosing schemes in glioblastoma cancer stem cell lines. J Neuro Oncol. 2012;109(1):45–52.
76 Chen J, Li Y, Yu TS, McKay RM, Burns DK, Kernie SG, et al. A restricted cell population propagates glioblastoma growth after chemotherapy. Nature. 2012;488(7412):522–6.
77 Lathia JD, Gallagher J, Myers JT, Li M, Vasanji A, McLendon RE, et al. Direct in vivo evidence for tumor propagation by glioblastoma cancer stem cells. PLoS One. 2011;6(9):24807.
78 Alfonso JCL, Talkenberger K, Seifert M, Klink B, Hawkins-Daarud A, Swanson KR, et al. The biology and mathematical modelling of glioma invasion: a review. J R Soc Interf. 2017;14(136):20170490.
79 Xu W, Li T, Gao L, Zheng J, Shao A, Zhang J. Efficacy and safety of long-term therapy for high-grade glioma with temozolomide: a meta-analysis. Oncotarget. 2017;8(31):51758–65.
80 Piccirillo SG, Binda E, Fiocco R, Vescovi AL, Shah K. Brain cancer stem cells. J Mol Med Berl. 2009;87(11):1087–95.
81 Heddleston JM, Li Z, Lathia JD, Bao S, Hjelmeland AB, Rich JN. Hypoxia inducible factors in cancer stem cells. Br J Cancer. 2010;102(5):789–95.
82 Chang WH, Lai AG. Aberrations in Notch-Hedgehog signalling reveal cancer stem cells harbouring conserved oncogenic properties associated with hypoxia and immunoevasion. Br J Cancer. 2019;121(8):666–78.
83 Hajizadeh F, Okoye I, Esmaily M, Ghasemi Chaleshtari M, Masjedi A, Azizi G, et al. Hypoxia inducible factors in the tumor microenvironment as therapeutic targets of cancer stem cells. Life Sci. 2019;237:116952.
84 Schöning JP, Monteiro M, Gu W. Drug resistance and cancer stem cells: the shared but distinct roles of hypoxia-inducible factors HIF1α and HIF2α. Clin Exp Pharmacol Physiol. 2017;44(2):153–61.
85 Vazifehmand R, Ali DS, Othman Z, Chau DM, Stanslas J, Shafa M, et al. The evaluation expression of non-coding RNAs in response to HSV-G47Δ oncolytic virus infection in glioblastoma multiforme cancer stem cells. J Neurovirol. 2022;28(4–6):566–82.
86 Lee YS, Dutta A. MicroRNAs in cancer. Annu Rev Pathol. 2009;4:199–227.
87 Londin E, Loher P, Telonis AG, Quann K, Clark P, Jing Y, et al. Analysis of 13 cell types reveals evidence for the expression of numerous novel primate- and tissue-specific microRNAs. Proc Natl Acad Sci U S A. 2015;112:1106–15.
88 Mercer TR, Dinger ME, Mattick JS. Long non-coding RNAs: insights into functions. Nat Rev Genet. 2009;10(3):155–9.
89 Zhang C, Zhang J, Hao J, Shi Z, Wang Y, Han L, et al. High level of miR-221/222 confers increased cell invasion and poor prognosis in glioma. J Transl Med. 2012;10:119,
90 Spitzweg C. Gene therapy in thyroid cancer. Horm Metab Res. 2009;41(6):500–9.
91 Spitzweg C, Morris JC. The sodium iodide symporter: its pathophysiological and therapeutic implications. Clin Endocrinol. 2002;57(5):559–74.
92 Spitzweg C, Dietz AB, O'Connor MK, Bergert ER, Tindall DJ, Young CY, et al. In vivo sodium iodide symporter gene therapy of prostate cancer. Gene Ther. 2001;8(20):1524–31.
93 Spellerberg R, Benli-Hoppe T, Kitzberger C, Berger S, Schmohl KA, Schwenk N, et al. Selective sodium iodide symporter (NIS) genetherapy of glioblastoma mediatedby EGFR-targeted lipopolyplexes. Mol Ther Oncolytics. 2021;23:432–46.
94 Schirrmacher V, Fournier P. Harnessing oncolytic virus-mediated antitumor immunity. Front Oncol. 2014;4:337.
95 Galluzzi L, Vitale I, Warren S, Adjemian S, Agostinis P, Martinez AB, et al. Consensus guidelines for the definition, detection and interpretation of immunogenic cell death. J Immunother Cancer. 2020;8(1):e000337.