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Glioblastoma Multiforme: An Evaluation of Existing and Alternative Treatment Modalities

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ABSTRACT

Glioblastoma Multiforme is one of the most aggressive brain tumours with very poor prognosis, low progression free survival rates and overall survival rates. This is predominantly due to the difficulty in transporting drugs across the blood brain barrier. Therefore, the need for more efficacious treatments is increasing. This paper explains the pathophysiology behind how signal transduction pathways leading from faults in the EGFRvIII and the IDH gene lead to gliomagenesis. It moves on to highlight and contrast conventional therapies such as Surgical Resection, Chemotherapy, Bevacizumab and Radiotherapy with novel, alternative therapies such as oncolytic virotherapy, photodynamic therapy and tumour treatment fields. A literature review was also conducted, wherein methods and results - specifically, the phase of trial, number of patients, treatment modality, median progression free survival, median overall survival and general comments- of five past research studies were explicated and interpreted for each GBM alternative treatment modalities - Photodynamic therapy, oncolytic virotherapy and tumour treatment fields. Each of the 5 clinical trial studies for each alternative treatment yielded varied results: The mean mOS (median Overall Survival) and mPFS (median Progression Free Survival) of patients were 15.3 months and 7.5 months for OV, 18.4 months and 16 months for PDT, and 19.9 months and 6 months for TTF respectively. This paper intends to provide an insight into the future of Glioblastoma Multiforme treatment to further improve its diagnosis, prognosis and treatment.

Introduction

Gliomas are a common type of primary brain tumour that are found most abundantly in glial cells such as astrocytes, oligodendrocytes and ependymal cells. Glioblastoma Multiforme (GBM) is the most frequently occurring malignant glioma, and is classified as a grade IV astrocytoma by the World Health Organisation (WHO). It is categorised as a Grade IV astrocytoma due to specific histological aspects such as cytologic atypia, anaplasia, increased mitotic activity, microvascular proliferation and necrosis. GBM patients also GBM is also divided into 4 main subtypes: proneural, neural, classical and mesenchymal. Due to its high metastatic potential, diffuse gliomas invade adjacent tissue creating secondary tumours. GBM has a low median survival rate; even patients treated with optimal therapy only have a median survival of approximately 12 months, with less than 25% of patients surviving up to 2 years and less than 10% of patients surviving up to 5 years. In addition, GBM tumours are considered to be one of the most aggressive, fatal brain neoplasms. GBM is particularly difficult to treat since the tumours are typically found within the blood brain barrier, which gives rise to problems with respect to standard drug delivery. Since the blood brain barrier has a low permeability, it restricts the passage of certain drugs and molecular therapeutics . Furthermore, due to its delayed diagnosis, there are few applicable treatment methods available for GBM. Conventional treatment involves surgical resection coupled with radiotherapy and temozolomide(TMZ). As a neoplasm with comparatively limited treatment options, research on promising, effective neuro-oncological approaches is ongoing. In this review, we intend to outline and evaluate

existing treatment modalities for GBM, as well as non-conventional immunotherapeutic treatments and their respective prospects towards future treatment of GBM.

Epidemiology

The occurrence of glioblastomas is dependent on a variety of factors ranging from demographics such as age, race and sex distribution, to others such as ethnicity, geographic and environmental factors. Since specific gliomas differ quite significantly with respect to their cytology, it is difficult to accurately estimate its incidence rate. With reference to the 2013 CBTRUS (Central Brain Tumour Registry of the United States) report, the incidence rate of GBM exceeds that of all other malignant CNS neoplasms. Its average age-adjusted incidence rate is approximately 3.19/100,000. With respect to the age demographic distribution of GBM, the trend holds that the incidence rate increases with age, with the median age being 64. The incidence rate is least common in children and adolescents, but is considerably higher amongst the age group of 75-84 years. The incidence rate in gender also shows a difference in the male population as compared to the female population (3.97/100,000 vs 2.53/100,000 respectively). Additionally, there is a stark variance in GBM incidence rate across the racial demographic - 3.45/100,000 for Whites, 1.67/100,000 for Blacks and API (Asian and Pacific Islander), and 1.48/100,000 for AIAN (American Indian and Alaska Native).

Pathophysiology & Gliomagenesis

There are different factors that are responsible for gene mutations. When oncogenes responsible for gliomagenesis such as Epidermal Growth Factor Receptors (EGFRvIII) and Isocitrate dehydrogenase(IDH1 & IDH2) are overexpressed, the first stage of gliomagenesis starts. Anti-oncogenes, genes that regulate cell arrest, cell apoptosis and cell cycle regulation, can undergo partial gene deletion which forms mutant oncogenes that can also initiate gliomagenesis.

EGFR, also known as epidermal growth factor receptor, is proto-oncogene commonly associated with unregulated cell proliferation. Although extensively found in high grade gliomas such as glioblastoma, EGFR is less characteristic of a low grade glioma such as oligodendroglioma. An aberrant variation known as EGFRvIII (ΔEGFR/de2-7) is formed when EGFR undergoes partial deletion of exons 2-7. As a result, 267 amino acids are no longer coded for.

Deregulation of EGFR signalling pathways gives rise to further EGFR gene amplification in the mRNA transcripts. Autocrine signalling is the first step in the deregulation of the signalling pathway; the cell produces signalling ligands (EGFR-specific) which bind to Receptor Tyrosine Kinases (RTK). This eventually results in sustained cell growth and proliferation. Signal transduction further involves a series of biochemical reactions specific to each signalling pathway.

For EGFR, this includes the Ras/Raf/MEK/ERK pathways. The completion of these reactions leads to the phosphorylation of certain transcription factors required for mRNA transcription and translation. As a result, the expression of certain genes is promoted. This also gives rise to the transactivation of EGFRvIII. Numerous copies of this gene are promoted, and this cycle repeats, causing uncontrolled cell proliferation.

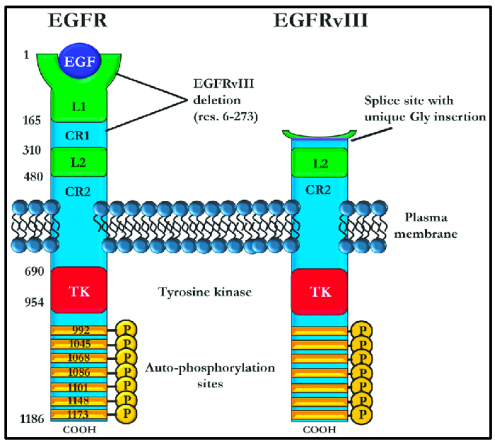

Figure 1. Structure of EGFR Vs EGFRvIII

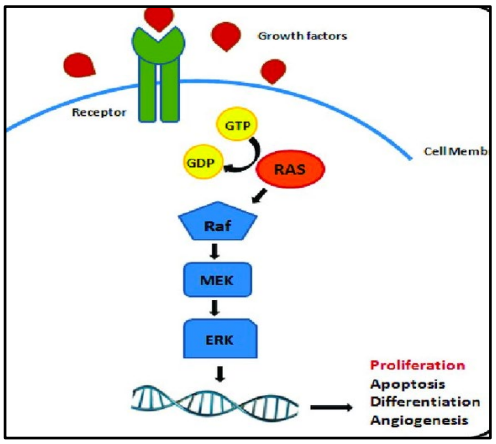

Figure 2. Depiction of Ras/Raf/MEK/ERK Cell signal transduction pathway

Isocitrate Dehydrogenases(IDHs) are homodimeric enzymes that aid in the oxidative decarboxylation of isocitrate to α-ketoglutarate, a metabolite, in the Krebs cycle of respiration. The IDH1 gene is present in the second chromosome of the human karyotype. Wild-type IDH1 codes for the codon that subsequently translates to the amino acid arginine. However, when this specific sequence is mutated, a different codon in the mRNA transcript is formed, and a different amino acid is coded for. As a result, a new polypeptide is translated altogether. When the mutant IDH1 gene codes for this different enzyme, it facilitates the breakdown of isocitrate to 2-hydroxyglutarate(2-HG), an oncometabolite. 2-HG affects DNA and histone demethylation that affects gene expression which leads to tumour progression.

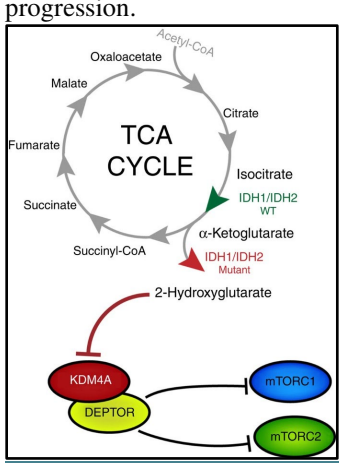

Figure 3. Krebs Cycle Pathway in the presence of mutant IDH gene

Current Treatments

Diagnosis of glioblastoma primarily relies on brain and spinal cord imaging to detect the presence of a tumour. Contemporary imaging techniques such as computerised tomography and magnetic resonance imaging are highly sensitive and reliable methods of investigation. However, a surgical biopsy may be used to confirm the diagnosis. Hypercellularity, nuclear atypia, microvascular angiogenesis, and cell necrosis are all pathological features that are characteristic for GBM. GBM is one of the most invasive tumours, which results in a substantially high potential for tumour recurrence. GBM cells also utilise autocrine and paracrine signalling, which makes the growth rate of GBM aggressive and all the more crucial to have an early diagnosis. If left untreated, glioblastomas can metastasize and become fatal in a matter of months or even weeks.

Surgical Resection

Cytoreductive surgery is a common approach to cancer treatment, which can be performed for several different types of malignant tumours. The process of surgical resection can be further divided into 3 stages. For GBM, specifically, the process begins with a biopsy which is then followed up by different resective procedures such as craniotomy, shunt placement/revision, awake surgery or Intraoperative Fluorescence(a relatively novel method). However, since GBM tumours infiltrate into adjacent tissue, these techniques do not result in complete excision of the neoplasm.

With the assistance of specialised medical tools, computerised guidance and imaging techniques, neurosurgeons are able to remove the bone flap of the brain to expose the brain through the process of a craniotomy. Some also employ stereotactic craniotomy: the usage of stereotactic frames for precise referencing of scalp landmarks. By using an appropriately shaped incision cut, the tumour as well as adjacent healthy tissue in the margin are able to be resected. Lastly, intraoperative fluorescence utilises the imaging agent 5-aminolevulinic acid(5-ALA), which allows gliomas to fluoresce under blue light to aid in surgical navigation. As a standard, patients are also subjected to adjuvant chemotherapy for up to 6 months to ensure remission of the cancer.

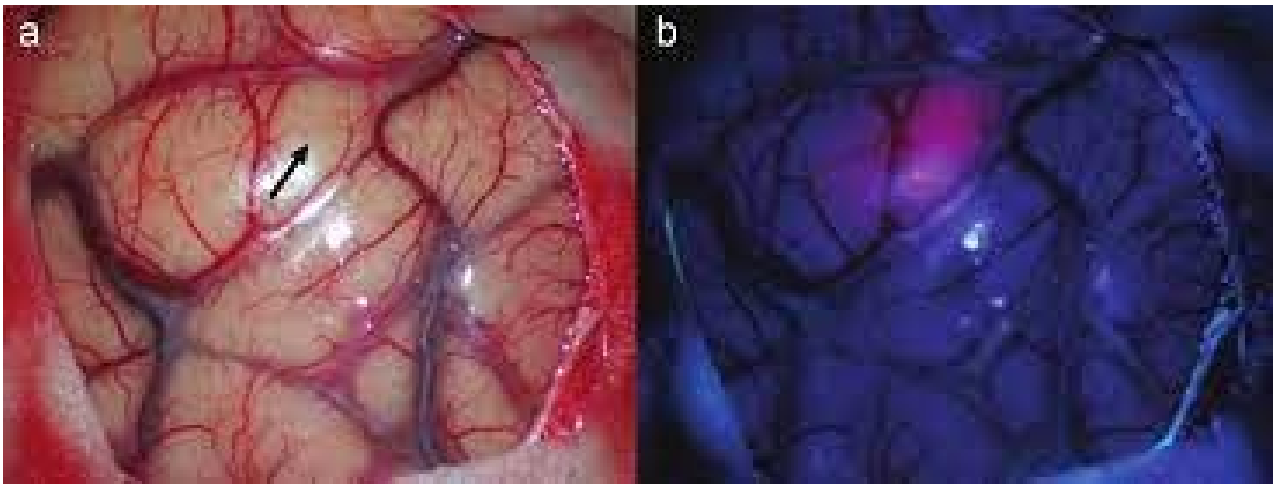

Figure 4. Normal Resection Vs 5-ALA Guided Resec-

Chemotherapy

The chemotherapeutic drug Temozolomide (TMZ) is an oral alkylating agent that is primarily used in the treatment of Glioblastoma Multiforme and Anaplastic Astrocytoma. Essentially, the drug works by inhibiting the division of cancer cells. Without cell division, the cancer can't progress and the tumour can't metastasize, thereby reducing the chances of death. TMZ can be used on its own, or concomitantly with radiotherapy. TMZ is usually administered once a day for around 6-7 weeks, often in addition to daily radiotherapy to improve efficacy. Side effects for temozolomide include fatigue, nausea, infection, constipation, low platelet count etc. A trial conducted by James Perry, M.D., of Sunnybrook Research Institute in Toronto tested the regimen in patients with glioblastoma, one of the most aggressive types of brain cancer. The trial, led by the Canadian Cancer Trials Group (CCTG), focused on patients over the age of 65. Because of concerns about serious side effects of chemotherapy, radiation alone has been the standard of care for patients aged 70 and older. In fact the radiation course was truncated to 3-4 weeks rather than the recommended 6 weeks. Median overall survival in patients treated with both radiation and temozolomide was 9.3 months, compared with 7.6 months in patients who received radiation therapy alone. The radiation and temozolomide combination also modestly improved

progression-free survival. The 1-year and 2-year survival rates were 37.8% and 10.4% with radiation plus temozolomide, versus 22.2% and 2.8% with radiation therapy alone.

Radiotherapy

For GBM, 6000 cGy radiation is used. At high doses like this, radiation damages the DNA of the cancerous cells, restricting them to grow and divide further. However, it may take weeks or months after the first radiation session for the damage caused to the DNA to have a substantial detrimental effect on the cells' potential to divide. The types of radiation can be power beams of X-rays, gamma rays or photons, that are aimed at destroying or shrinking the cancerous cells in the tumour. However, imprecisions with directing radiation beams will naturally lead to damage of cells in surrounding healthy tissue. A solution to this problem is the use of Intensity-modulated radiation therapy(IMRT), which utilises computer-controlled linear accelerators that operate at high precision to accurately direct the radiation beams, and advanced imaging techniques. Another method is Stereotactic radiosurgery, which positions radiation sources closer to the tumour to give higher doses in fewer total radiotherapy sessions. In order to minimise the effects of radiation on healthy cells, radiotherapy is split into fractions, which are sessions of radiation beams of small doses. Like any other treatment, radiotherapy does have drawbacks. High doses could result in chromosomal damage of healthy cells. There will be a reduced white blood cell count. Patients may likely experience side effects like vomiting, diarrhoea, fatigue, temporarily compromised immune responses etc.

In a study conducted by Abdolazim Pashaki et al., 68 patients(45 males and 23 females) with advanced stages of GBM were treated with resection, and given post-operative radiotherapy followed by adjuvant chemotherapy. After 19 months the study revealed the following results: 39 patients showed evidence of GBM progression, of which 36 died. Overall, the median patient survival was 16 months, but only around 6 months for the median of patients with progression free survival. Furthermore, the study showed that patients who were subjected to higher doses of radiotherapy (>60 Gy) experienced lower GBM progression rates. The study showed that stronger radiation doses, although currently showing inconclusive results, have the potential to improve patient prognosis and survival rates.

Bevacizumab

GBM tumours divide and proliferate through the process of angiogenesis; at a certain stage during tumorigenesis (before the tumour can grow 1-2mm), vascularisation begins: the process of sprouting of new capillaries/blood vessels from the existing vasculature. Due to the tumour's high metabolic rates, it requires oxygen and additional nutrients for further growth, leading to an oxygen deficit. VEGF-A(Vascular Endothelial Growth Factor) is a pro-angiogenic signal protein that promotes angiogenesis. Under hypoxic conditions in GBM tumours, the hypoxia inducible factor(HIF) binds to the VEGF gene, resulting in the transcription of the VEGF gene. VEGF then binds to extracellular tyrosine kinase receptors: VEGFR-1/Flt-1, VEGFR-1, VEGFR-2, and VEGFR-2/KDR. Bevacizumab's primary function is to neutralise VEGF-A by binding to its primary receptor VEGFR-2, and preventing further proliferation of blood vessels. This makes Bevacizumab an effective antiangiogenic therapeutic.

In standard treatments, bevacizumab is used concomitantly with chemotherapy in order to enhance its efficacy. The maximum-tolerated dose of bevacizumab is 20 mg/kg, at which 25% of patients suffer from grade ≥3 toxicity (on a scale of 1–5, according to the Common Toxicity Criteria) including headache, nausea, and vomiting.

Alternative Therapies

GBM remains to be one of the most frequent and aggressive brain tumours. Despite having multimodal therapeutic strategies, the prognosis remains poor. There are several reasons behind the lack of scope and efficacy of conventional methods in the treatment of GBM: its high invasiveness, natural resistance to several chemotherapeutics, protection from the blood brain barrier, and most importantly, its intratumoral heterogeneity. Many of the prospective and unconventional treatment modalities such as antiangiogenic therapy (Bevacizumab), Oncolytic virotherapy, Tumour Treating Fields, Photodynamic Therapy are intended to overcome the problems caused by GBM.

Oncolytic Virotherapy

Major obstacles encountered in GBM treatment such as its inherent resistance to chemotherapy and radiotherapy, while also being protected by the blood brain barrier, have encouraged scientists to look beyond conventional methods and have helped them come across alternative treatments such as Oncolytic Viral Therapy or Virotherapy (OV). OV is an immunotherapeutic alternative that utilises oncolytic viruses that directly lyse tumour cells and stimulate immune responses. Examples of oncolytic viruses are Adenovirus, Herpes simplex virus, Maraba virus, Measles, Newcastle Disease Virus, Picornavirus, Reovirus, Vaccinia virus and Vesicular stomatitis virus. The viruses differ in their primary affinity to different molecules and the source of their tropism. Some possess a natural affinity towards certain tumour cells, while others can be genetically engineered to exhibit selective oncotropism. Typical GBM cells have weakened antiviral defences, which makes OV effective. Encoding gene products or therapeutic payloads in the virus backbones can diminish their focus on attacking healthy cells, and deliver these therapeutic payloads through polymeric nanoparticles containing mRNA strands, small molecules, proteins, nucleic acids, and diagnostic agents. After the viruses initiate oncolysis, the cancer cells release antigens which stimulate immune responses to promote oncolysis of the remaining tumour cells.

To overcome the intratumoral variability of GBM cells, stratification of patients based on the receptors present in the tumour can improve the efficacy of the treatment. The viruses are generally administered through intraarterial port systems in the carotid artery. They can also be administered through insertion of tumour-specific promoters, which also gives rise to viral replication.

Photodynamic Therapy

Photodynamic therapy (PDT) is a two-stage treatment that employs a combination of drugs (photosensitizer molecules-PS) and a wavelength-specific light source to destroy cancerous/precancerous cells. PS molecules are typically non toxic until activated by light. However, after photoactivation it becomes toxic to a target tissue. Common PS molecules that are used in the treatment of GBM include Talaporfin sodium, Porfimer sodium, 5-Aminolevulinic acid (5-ALA) and Temoporfin.

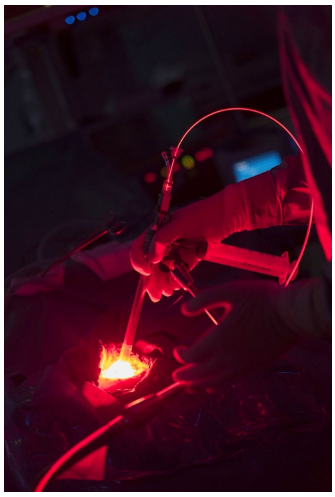

Figure 5. Photodynamic Therapy

Photodynamic therapy is a two-step process. Firstly, the patient receives a photosensitizer. The drug may be administered orally, spread on the skin, or given through an IV, depending on the location of the tumour. After 2-3 days, most of the drug will have left normal cells but remain in cancer or precancer cells. The tumour is then exposed to the light source which causes the PS to produce a form of oxygen that helps destroy cancer cells. Although PS molecules are administered in small doses (0.15 - 20 mg/kg), the majority of them have side effects varying from skin sensitization to nausea and anaemia.

In essence, PDT utilises Reactive Oxygen Species(ROS) to initiate programmed cell death(PCD) and decrease the tumour's metastatic potential. In typical GBM tumour cells, the enzyme catalase in peroxisomes facilitates biochemical decompositions which results in relatively high cell antioxidant levels to counter oxidative stress created by ROS. This further allows ECM-detached cells to readily metastasize to adjacent tissue and other parts of the body. After administration, the photosensitiser(PS) molecules get preferentially absorbed by the tumours cells. They exist in the singlet state with all paired electrons. When a beam of light of a specific wavelength(in the range of visible and infrared light) is shone, the electrons in the ground state enter a higher energy orbital, resulting in a singlet excited PS, which is unstable in nature. To counter this instability, the singlet excited PS emits energy in the form of fluorescence or internal conversion(production of heat energy). This allows it to enter the triplet state, which is more stable in nature. The longer lifetime of these molecules should suffice for a successful collision with molecular oxygen, transferring energy in the process. Ultimately, the oxygen transforms into singlet ROS. The ROS formed by PDT inactivates the peroxisomal catalase. Due to this, the antioxidant activity is no longer regulated, and decreases. This will lead to Type I PCD, and will not allow the tumour to metastasize.

Tumour Treatment Fields

Tumour treating Fields(TTFields) is a non-invasive novel therapy that makes use of low intensity alternating electric fields to disrupt mitotic activity in the GBM tumour cells, subsequently inducing cellular apoptosis. As shown by Kirson et al., the optimum range for frequency of alternating electric fields to successfully promote antimitotic behaviour is 100kHz-300kHz.

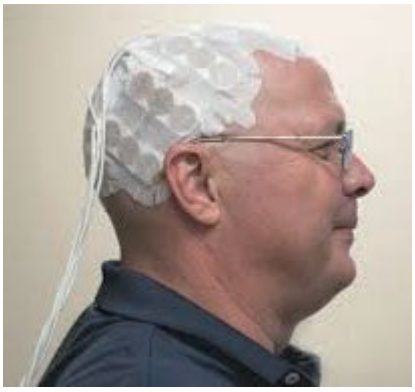

Figure 6. Tumour Treatment

During metaphase, the second stage of mitotic cell division, α-tubulin and β-tubulin dimers polymerise to form microtubules, which make up the spindle fibre that connect to the chromosomes' kinetochores situated along the metaphase plate. Additionally, some intermediate filaments called septin molecules are associated with the contractile apparatus during cytokinesis; they, along with other proteins, aid in developing the cytokinetic 'cleavage furrow'. Both septin molecules as well as the tubulin dimers exhibit dipole moments. When subjected to TTFields, these molecules demonstrate two phenomena: dipole alignment and dielectrophoresis. Dipoles are molecules that consist of a separated charge and when subjected to high frequency electric currents they undergo dipole alignment, which refers to the alignment of dipoles along electric field lines. The tubulin dimers that form spindle fibres, when subjected to the TTfields, align along the field lines. The high frequency of the electric current results in restricted motion of these molecules, and hence interferes with the formation of spindle fibres eventually leading to metaphase arrest, membrane blebbing and apoptosis. In some cases, abnormal spindle fibre formation is completed even after exposure to TTfields. This can ultimately lead to non-uniform DNA segregation to daughter cells, induced apoptosis and programmed cell death. In certain cells that survive past metaphase and reach early telophase, the cytokinetic furrow starts to develop. Due to the furrow's hourglass shape, a non-uniform alternating electric field is exhibited, causing dielectrophoresis. Molecules exhibit dielectrophoretic activity when subjected to certain forces that cause them to move towards a region of relatively high electric flux density. This causes cell fragmentation and structural disruption.

Cells that are oriented perpendicular to the TTfields are unaffected. Hence, TTF is administered through two pairs of transducer arrays positioned perpendicular to each other. This ensures that maximum tumour cells are targeted to increase the efficacy of the treatment. Another optimization to TTF treatment is by ensuring that the electric fields are tuned to a specific frequency based on cell type and patient history so that it does not affect adjacent somatic cells.

Clinical Trials And Results

Oncolytic Virotherapy

In a clinical trial conducted by Desjardins et al, the efficacy of recombinant nonpathogenic polio-rhinovirus chimera (PVSRIPO) in dose escalation phases and dose expansion phases was examined. The goal of the trial was to determine the toxicity profile of PVSRIPO. The trial was conducted from May 2012 to May 2017 with 61 patients. PVSRIPO was administered through a catheter by convection enhanced intratumoral delivery to adults with recurrent supratentorial grade IV malignant glioma. MRI scans were done after specific times after

the intratumoral infusion. The study adhered to the levels of toxicity as defined by the Common Toxicity Criteria for Adverse Events. Among all 61 patients, the median overall survival rate for patients who received PVSRIPO infusions was 12.5 months (95% CI). However, the median overall survival rate was only 11.3 months(95% CI) in the control group. Additionally, the median overall survival rate was 6.6 months(95% CI) in the NOVO-100A treatment group; this group utilised standard tumour treatment fields therapy, which included alternating electrical current applied to electrodes on the patients' heads. OS(overall survival rate) in the experimental group was 21% at 24 months, and reached a plateau point. OS in the control group declined from 14% at 24months to 4% at 36 months. The OS in the NOVOTTF-100A group decreased from 8% in 24 months to 3% in 36 months. Additionally, some patients, administered dose level 5, were subjected to lomustine therapy, after 7 months, if there was a detection of rGBM tumours. Another 37 patients were subjected to other therapies such as TMZ, lomustine and others. Therefore, in order to counteract the side effects of some patients, the trial utilised other therapies. In doing so, the experiment's results, especially median progression free survival rates, would be slightly inconsistent.

Table 1. Clinical Trial Results for Oncolytic Virotherapy

Authors	Phase of trial	No. of Patients	Treatment	Median Survival(months) PF	Overall	General Comments
Desjardins et al.	I, II(ongoing)	61	PVSRIPO (Poliovirus)	NR	12.5	NR
Fares et al.	I	12	NSC-CRAd-S-pk7	9·1	18.4	Few adverse events were reported in the patients excluding one outlier who developed grade 3 meningitis. No treatment related deaths were reported either.
Todo et al.	I/IIa	13	triple-mutated oncolytic herpes simplex virus type 1	8.0	7.3	Adverse events occurred in 12/13 patients. The most common G47Δ-related adverse events were fever, headache and vomiting.
Steiner et al.	Non-randomised clinical trial	23	Vaccination: Newcastle disease virus + gamma irradiation	9.2	23.0	Post-operative vaccination with virus-modified autologous tumour cells improved the prognosis of patients with glioblastomas. This was substantiated by the antitumour response.
Geletneky et al.	I/IIa	18	H1-Parvovirus	3.6	15.2	Adverse events were reported after treatment: reduced consciousness, occlusion of ventricle catheters and reduction in PFS to 27% after 6 months

Additionally, there are many side effects associated with oncolytic virotherapy. Based on the dosage level they were subjected to, patients experienced either fatigue grade 1, gait disturbance grade 1, cognitive disturbance grade 2, dysphasia grade 1 and 2, paresthesia grade 1 and 2, pyramidal tract syndrome grade 2 and 3, seizure grade 1 and 2, or psychiatric disorder: confusion grade 1. Another study conducted by Fares et al.(n=12) showed that 1 patient experienced viral meningitis grade 3. In a trial conducted by Lun et al.(n=14),

the reovirus, unlike the VSV Δ M51 virus, did not lead to regression of bilateral gliomas in an immunocompetent racine glioma model. Furthermore, the exact method by which intravenous VSV Δ M51 entered the single cells was unknown; overall, there is a wide scope for research in OVT to determine how each virus specifically functions. The effectiveness of PDT can be augmented overall by eliminating the use of additional control therapies specific to different patients, and focus on specifying certain control treatments for the entire patient population.

Photodynamic Therapy

A Photodynamic therapy study was conducted by Yoshihiro M et al. with the purpose of determining the efficacy and safety of intraoperative PDT using talaporfin sodium and irradiation using a 664-nm semiconductor laser in patients with primary malignant brain tumours, especially GBM. The study involved a group of 22 patients with newly diagnosed or recurrent tumours, with roughly 60% being newly diagnosed glioblastomas. Each patient was administered a single 40 mg/m^2 dose of talaporfin sodium intravenously. 22-27 hours after resection, the tumour cavity was irradiated to activate the photosensitizer. 12-month overall survival, PFS6 and 6-month local PFS rates were recorded and were found to be 95.5%, 91% and 91% respectively. Although inconsistent, the treatment did show a few side effects including skin rashes, blisters and erythema in around 7.5% of the patients. The treatment's effect on the skin could be attributed to the use of talaporfin sodium and was relatively mild, fully disappearing within 15 days of the administration of the photosensitizer in all patients.

Table 2. Clinical Trial Results for Photodynamic Therapy

Authors	Phase of trial	No. of Patients	Treatment	Median Survival(months) PF	Overall	General comments
Muragaki et al.	II	22	Resection + Talaporfin sodium (40 mg/m^2)	12.0	24.8	There were a few isolated side effects on the skin such as rashes and blisters
Vermandel et al	I	10	(5-ALA - Guided Resection) + Intraoperative PDT	17.1	23.1	There were no serious adverse effects reported.
Akimoto et al.	Preliminary Clinical Report	14	Talaporfin Sodium	23.0	26.0	Remaining 3 patients survived for more than 3 years with a good KPS. 8 patients with recurrent tumours that received PDT had a response rate of 25.0%. The approximate survival time was noted to be only 9 months following PDT.
Eljamel et al.	III	27(14 control)	Photofrin fluorescence guided Resection + PDT	12.0	8.6	The average points KPS was 20 points ($p<0.05$). There were no differences in complications or hospital stay between the two groups.
Muller et al.	III, Evaluation of Randomised trials	112	Resection + PDT (Porfimer Sodium)	NR	9.7	75% of the patients had no postoperative complications.

From the studies discussed, the combination of pre/intra/post operative PDT (with talaporfin sodium) and gross total or maximal resection may be considered as a potentially effective and sufficiently safe option for management of GBMs. The inclusion of PDT in a combined treatment strategy shows a mostly positive impact on OS and local tumour control, particularly in patients with newly diagnosed GBMs. Certain clinical trials (Muragaki et al., n =22) did report isolated side effects such as skin irritations but no major disruptions to the overall Quality of Life of the patients. Muller et al.'s trial (n=112) also reported no postoperative complications in 75% of the patients indicating both the efficacy and safety of the treatment. From the reviewed data PDT seems to be a promising treatment that can potentially save or at the least prolong the lives of patients with the best possible QoL but more clinical trials must be conducted with a larger sample size to accurately determine the safest dose and efficacy of PDT.

Tumour Treatment Fields

In a randomised clinical phase-3 trial analysis conducted by Stupp et al., the effectiveness of TTFields in combination with standard treatment of GBM- temozolomide - was studied through the health-related quality of life (HRQoL) standard. This study consisted of 695 patients, and lasted from July 2009 to November 2014. This study involved 2 groups: 1 group that was administered combined TTFields and TMZ therapy(466 patients), and the other that was administered solely with TMZ therapy(229 patients). HRQoL was evaluated using the European Organisation for Research and Treatment of Cancer(EORTC) brain module and questionnaires, time to deterioration approaches, and median deterioration free survival months. HRQoL was assessed based on 9 predefined factors. Post study completion, both groups compared the improvement of each of the 9 HRQoL characteristics during progression free time. For the group treated with TTfields as well as TMZ, all the 9 HQRoL characteristics were remedied by a percentage of patients higher than those of the group treated with only TMZ. In addition, the hazard ratio (95%) showed that physical, cognitive, role, social and emotional functioning occurred for greater numbers of median months of deterioration free survival for the group treated with TTFields. Like the three previous therapies, TTFields also yielded numerous side effects. In the study conducted by Stupp et al.(n=695), the group subjected to TTF and TMZ had 48% of patients who experienced more than 1 adverse event. The group subjected to TMZ alone had 44% of patients who experienced more than 1 adverse event. Adverse events were categorised based on body system and severity, and included the following: blood and lymphatic system disorders, thrombocytopenia, gastrointestinal disorders, asthenia, fatigue and gait disturbance, infections, injury, poisoning and procedural complications, metabolism and nutrition disorders, musculoskeletal and connective tissue disorders, seizures, and respiratory, thoracic and mediastinal disorders. Hence, although the TTF+TMZ group yielded higher OS and PFS6 rates, the side effects were greater and included a larger patient population which would decrease HRQoL. Another study conducted by Kim et al(n=39) showed that TTF yielded significantly higher overall survival rate and 6 month progression free survival rates, but had a relatively small sample size. Furthermore, TTF was not shown to result in increased toxicity or a higher percentage incidence of adverse events. Since the data was based on a subgroup analysis of the Ef-14 trial, however, it would be prone to type I errors. In another study conducted by Kesari et al.(n=466), some patients experienced more than 1 adverse event(blood and lymphatic disorders, gastrointestinal disorders, infections and infestations, injury, poisoning and procedural complications, metabolism and nutrition disorders, musculoskeletal and connective tissue disorders, psychiatric disorders and vascular disorders.

Table 3. Clinical Trial Results for Tumour Treatment Fields Therapy

Authors	Phase of trial	No. of Patients	Therapy combination	Median Survival(months)		General comments
				PF	Overall	
Stupp et al.	III(EF-14 Trial)	695	TTF+TMZ	6.7	20.9	The control group(TMZ alone) had a median PFS of 4mo and a median OS of 16mo.
Kim et al.	III	39	TTF+TMZ	6.2	27.2	The control group(TMZ alone) had a median PFS of 4.2mo and a median OS of 15.2mo.
Ballo et al.	III	340	TTF	8.1	24.3	The control group(TMZ alone) had a median PFS 7.9mo of and a median OS of 21.6mo
Kesari et al.	III(EF-14 trial)	466 (228 second line treatment)	TTF+TMZ	7.1	20.5	The control group(chemotherapy alone) had a median PFS of 4mo and a median OS of 15.6mo.
Stupp et al.	III	120	TTF+TMZ	2.2	6.6	The control group(TMZ alone) had a median PFS of 2.1mo and a median OS of 6.0mo.

In summary, the above studies did show that OS and PFS of the TTF+TMZ test groups showed a better outcome (although associated with side effects) compared to the control group. Since some studies were taken from a relatively small sample size, future studies should aim to target larger sample sizes, attempt to reduce side effects, and focus on determining optimum electric field frequency based on patient history and underlying conditions. For further optimisation, tumour treating fields can be adapted to specific types of tumours by tuning the frequency of the electric fields to specific cell types.

Discussion

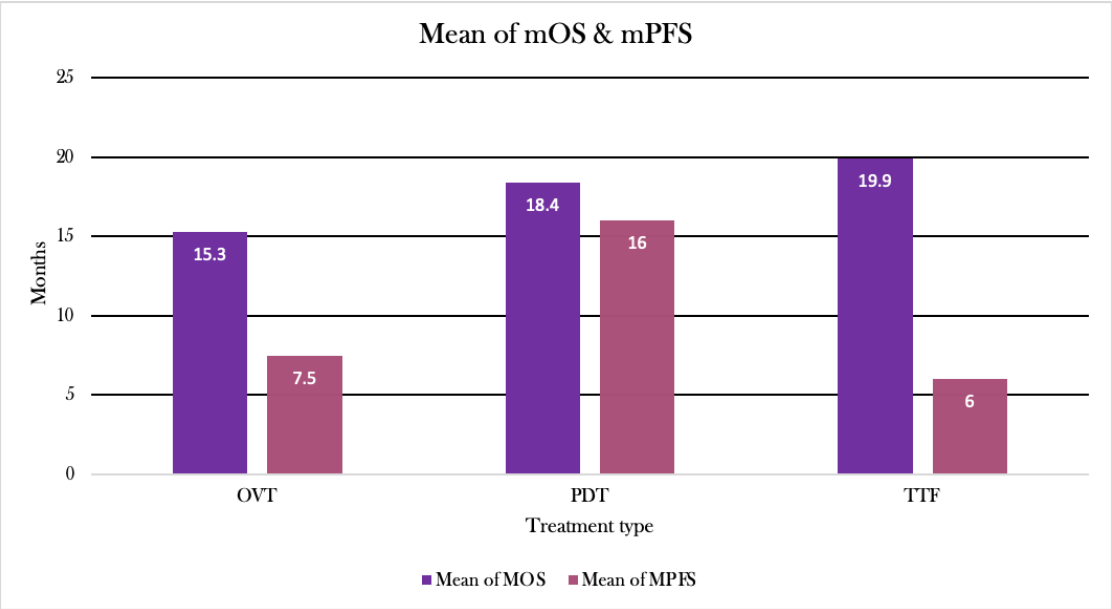

Figure 7. Graph of means of mOS(median overall survival) and mPFS(median progression-free survival)

Quantitative Analysis

Using the values for median PFS and median OS, the average across the clinical trials that were used demonstrate the efficacy of the treatments was calculated, which were used demonstrate the efficacy. The above data allows us to interpret the QoL (Quality of Life) of the patients for each type of treatment. TTF had a mean mOS of 19.9mo and a mean mPFS of 6mo, which indicates that the patients experienced a fairly large period of time where the glioblastoma progressed, thus implying a poorer QoL. In contrast, PDT has a fairly similar mean mOS - 18.4mo - but an mPFS that was almost 3 times as that of TTF - 16mo. This indicates that although the mean mOS for PDT was less than that of TTF, patients administered to PDT treatments experienced a relatively shorter period of time where the glioblastoma progressed, indicating a better Qol. Finally, OVT had a mean mOS of 15.3mo and a mean mPFS of 7.5mo. OVT's mOS was the least of the 3 treatments, indicating that patients administered to OVT treatments lived for the shortest period of time after administration. However, patients administered to OVT experienced a larger mean mPFS than that of TTF, signifying that the patients underwent a shorter period of time with the glioblastoma progressing. For this analysis, only 5 studies per treatment were used to calculate the mean and standard deviation, which is a fairly small sample size to generalise results. Since these treatments are relatively novel, there are not many ongoing studies that focus on the utilisation of these treatment modalities in clinical trials. In the context of cancer patients, the primary goal should be to use treatment modalities that can completely cure patients of their condition. However, in the case of GBM this is usually a very high standard to set. Medicine nowadays is focused predominantly on increasing the efficacy of treatments by alleviating side effects and improving QoL of these patients.

Conclusion and Further Implications

As discussed in this paper, Glioblastoma Multiforme is one of the most aggressive brain tumours with very poor prognosis, low progression free survival rates and overall survival rates. Furthemore, GBM is commonly diagnosed when the tumour has already progressed to advanced stages (such as Stage IV), reducing the prognosis of patients to a greater extent. This paper has contrasted conventional therapies such as Surgical Resection, Chemotherapy, and Radiotherapy with novel therapies such as Oncolytic virotherapy, photodynamic therapy

and tumour treatment fields. It should also be noted that for the most effective results, they should be used in conjunction with conventional therapy. Although these therapies are well established, their usage in the treatment of GBM is still quite novel. There are multiple variations to the same therapies; for instance, OVT utilises different types of viruses that are required to be tested individually to determine their efficacy. Similarly, in the case of TTF, different types of delivery methods are required to be investigated adjuvantly with conventional treatments to determine the most effective way of using them cooperatively. Thus, there are very minimal clinical trials in advanced stages that collect sufficient data for a specific treatment or therapeutic strategy (multiple treatments used in conjunction with each other) for their reported mPFS rates and mOS to be statistically significant. Additionally, the majority of the existing clinical trials utilise in-vitro rather than in-vivo techniques. Immunotherapeutic, chemotherapeutic and radiotherapeutic treatments have been gradually advancing in recent decades with research and technological advancements, but further, adequate research is still required for these alternative therapies to become mainstream treatment modalities. In addition, novel therapies that have been described in this paper are some amongst many: for example, there is scope for other treatment modalities such as those involving the targeting of signalling pathways, stem cell therapy etc. As this paper has highlighted, existing medicine can only help in extending the lives of patients by a few months; hence, it is crucial that researchers and clinicians alike continue to work towards finding new methods to combat GBM.

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