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Precision Medicine at a Nanoscale: Targeted Nanotechnology as a Promising Strategy for Glioblastoma Therapy

Pragati Kumbhar[1], Shivam Waghmare[2]

[1,2]Department of Biotechnology, National Institute of Pharmaceutical Education and Research– Hajipur 844102, India
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ABSTRACT:

Glioblastoma is the deadliest cancer worldwide. Due to its location in the brain and resistance to conventional therapies, glioblastoma is a particularly deadly and aggressive type of brain cancer that is challenging to treat. By enabling precise drug and therapeutic agent delivery to the tumour site, avoiding the blood-brain barrier, as well as minimising negative effects, targeted nanotechnology presents a potential therapy method for glioblastoma. A variety of drugs or therapeutic agents can be carried by nanoparticles, enabling a combination of treatments. They can also be utilised in non-invasive cancer treatments like magnetic hyperthermia and photothermal therapy, which use heat to kill cancer cells. Additionally, nanoparticles can be created to target particular tumour markers, enabling personalised treatment for different patients.

Content:

Introduction:

With the highest rates of mortality and morbidity among gliomas, glioblastomas are the most deadly and aggressive tumours. Glioblastoma patients are currently medicated with radiation therapy and concomitant chemotherapy with the medication temozolomide (TMZ), followed by the maximum safe tumour resection.[1] GBM, is the most typical grade IV astrocytoma and incurable malignant neoplasm in grown-ups, responsible for 54% of all gliomas as well as 16% of primary brain tumours, according to the World Health Organization[2] Glioblastomas account for roughly 16% of all primary malignant brain tumours harming the CNS and the brain GBMs.[3] The most prevalent age range for GBM patients is 45 to 70. The typical diagnostic age is 64. The condition affects people of all ages and genders, with men having a slightly greater risk than women. The genetic makeup of GBM causes resistance to radiation and TMZ, according to a recent study, yet medication crossing the BBB continues to be a critical therapeutic hurdle for GBM (BBB). Today, there is a ray of hope for GBM patients because of the nanotechnology platform.[4]

Numerous nanomaterials have been researched as therapeutic agent carriers for the treatment of GBMs, including liposomes, nanoemulsions, polymeric micelles, and iron oxide nanoparticles (IONP).[5] The last 10 years have seen substantial research into the creation of new technologies based on nanometer-sized particles (nanotechnology) for the treatment of cancer, and this strategy has promise for the detection and management of gliomas. Recent developments in proteomics and genomics have revealed distinct molecular signatures for each type of tumour, enabling new avenues for medicines that uniquely target and eradicate tumour cells.[6]

Drug delivery methods based on nanoparticles:

The brain cancer glioblastoma is extremely aggressive and challenging to treat. It is difficult to provide drugs to the BBB-protected tumour tissue in the brain, which makes it one of the key obstacles in treating glioblastoma. The BBB is a highly selective barrier that prevents many medications from entering the brain. Numerous drug delivery techniques have been developed to get around this obstacle and deliver medications to the glioblastoma tumour.

Nanoparticles are tiny particles that can be loaded with drugs and designed to pass the BBB and target cancer. They can cross the physiology of the BBB by cheating with glial cells i.e., projections of astrocytes. They can be engineered to release drugs slowly and can be designed to specifically target tumour cell receptors. To allow therapeutic medications to be delivered across the BBB, a wide range of nanoparticles have been developed. Since they can be delivered intracerebrally and gradually distribute their content, nanoparticles can get past the BBB's barrier. When administered systemically, nanoparticles may protect the loaded medications from degradation.[7]

Zinc Oxide Nanoparticles (ZnONPs)

Their surface characteristics suggest ZnONPs as a potential cancer therapeutic agent. The ZnO nanoparticles were cytotoxic to the human glioma cell lines like U87, LNZ308, LN18, as well as LN229, but there wasn't impact on healthy human astrocytes.[8] A metal oxide that is significantly smaller than many other organic materials is zinc oxide (ZnO). This substance is frequently used as an additive in many different types of materials and goods. ZnO can also photocatalyst reactions and oxidise substances in prokaryotic and eukaryotic cells. By the external emission of reactive oxygen species (ROS), ZnO uses multifunctional nanoplatforms to attack malignant cells from the outside (ROS).[9]

PLGA

Materials made of synthetic polymers hold promise for use in drug delivery systems. One of the most extensively researched polyesters is PLGA, which is made from glycolic acid and lactic acid. To treat the GBM, PLGA NPs that carry a chemotherapeutic medication have been investigated. Since TMZ is one of the most effective GBM medications currently being utilized in clinical trials, its encapsulation into nanoparticles (NPs) may represent a potential approach to treating GBM.[10] Excellent drug loading capacity as well as prolong and controlled released of an entrapped drug, great bioavailability, well-established and practical NPs preparation methods, appropriate bulk and surface characteristics for cell-particle interactions, and FDA approval for spe1cific applications are just a few of the impressive advantages that PLGA NPs have over other drug carriers. [11]

Silver Nanoparticles

In the treatment of glioblastoma, silver nanoparticles may be applied alone or in conjunction with any other substance. Chemically generated AgNPs exhibited suppress cell growth, against the commercial GBM cell line U87, resulting in a 35% drop-in development rate or rate of growth vs healthy or placebo-treated cells. AgNPs were also efficient against GBM when combined with other cytotoxic substances.[12] When used in comparison to the U87MG cell line, AgNPs saturated with a green alginate-chitosan combination had a substantial antiproliferative effect, inducing significant Damaging to the DNA, oxidative stress, and mitochondrial dysfunction with apoptosis.[13]

Quantum Dots

Semiconducting nanomaterials with a diameter of less than 20 nm are known as quantum dots (QDs). GQDs are now being used in the realm of neuroscience, particularly as benign labelling compounds for human neural stem cells that do not interfere with the capacity of cells to self-renew. The BBB can be crossed by GQDs due to their incredibly small (20 nm) size, allowing for the extremely strict as well as selective introduction of chemicals circulation in the blood. Capacity of crossing BBB is very significant in the cure for brain tumours such as GBM, the most severe kind of glioma.[14]

Magnetic Nanoparticles

Due to their distinct physical characteristics and inherent abilities, magnetic nanoparticles (MNPs) have become a potential prognostic platform for GBM treatment. As a result, innovative methods utilising MNPs are being developed to increase the effectiveness of current therapeutic techniques such as chemotherapy, radiotherapy, and others.[15] For guided glioma surgery and multimodal imaging, a photothermal nanoprobe which contains with macrophage capable of crossing the BBB and accumulating in deep gliomas is employed. For example MFe3O4-Cy5.5 is the one photothermal nanoprobe which is able to pass the BBB.[16]

Major Problems in Diagnosis and prognosis of glioblastoma

The absence of efficient diagnostic methods is one of the major issues in managing glioblastoma. Nowadays, neurological examinations and neuroimaging techniques are used as the primary diagnostic tools for glioma identification, but only after the disease has already progressed significantly. Glioblastoma symptoms can resemble those of other brain conditions like a stroke or an infection. Because of this, it may be challenging for doctors to diagnose a patient accurately based solely on symptoms.[17] Since the 1960s, more than 116 cases of GBM have been connected to radiation exposure, and it has been estimated, approximated, or projected that the overall probability of obtaining GBM following irradiation is 2.5%. In imaging techniques done on persons suspected of having brain tumours, invasive treatments like catheter angiography and non-invasive exams like CT and MRI scans are employed in the visualisation of tumours.[18] The diagnosis of glioblastoma frequently occurs after the tumour has already spread widely. This increases the difficulty of treatment and lowers the likelihood of success.

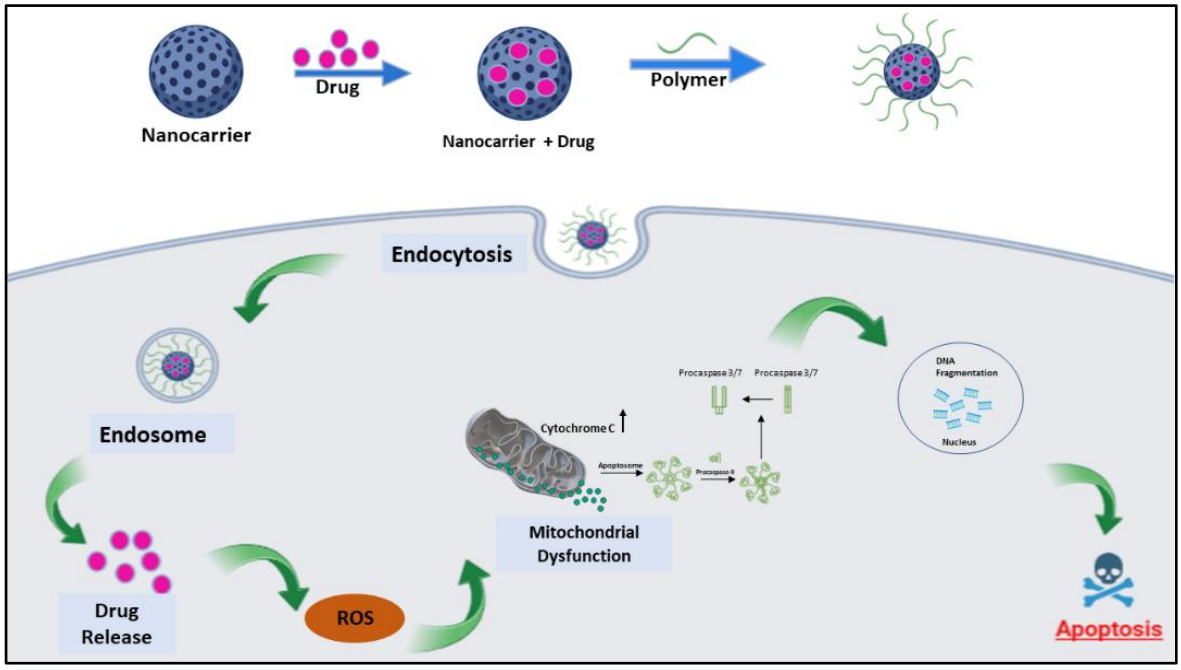
Glioblastoma prognosis is still difficult because of the disease's complexity and the limitations of available treatments. One of the most critical features of GBM is tumour heterogeneity. GBM is a highly heterogeneous tumour, which means that the tumour cells can differ significantly in their genetic makeup and behaviour. As a result, it is challenging to predict how a patient's tumour will respond to therapy and how quickly it will grow. Intertumoral heterogeneity, which allows tumours to be classified into different molecular subtypes, is essentially defined by discrete genetic mutations that occur in separate tumours that arise from the same organ.[19] Spatial heterogeneity and the clinical progression of GBM are two different ways to measure tumour heterogeneity (longitudinal heterogeneity). Even if samples are taken from various locations at the same time, molecular techniques can identify clonal and subclonal alterations to describe tumour evolution (spatial-temporal heterogeneity).[20] GBM is particularly resistant to most treatments due to its heterogeneous nature, which is connected to strong clonal plasticity and the presence of cancer stem cells that are resistant to TMZ- and RT-induced cell death.[21] Radiation and chemotherapy-resistant glioblastoma is complicated and mediated by several signalling pathways, in addition to the Wnt, Shh, NF-B, DDR, and MAPK pathways. Therefore, further research into treatments that are administered to resistant GSC populations and target these dysregulated pathways is necessary.[22] It is challenging to completely remove the tumour through surgery because glioblastoma cells are extremely invasive and can spread quickly throughout the brain. GBM invasion is caused by an ongoing bidirectional connection between tumour cells and their surroundings. Numerous ECM (Extracellular matrix) elements, fluids, soluble substances like chemokines and cytokines. Moreover, cells like neurons, astrocytes, oligodendrocytes make up the microenvironment [23]

How nanoparticles deliver drug or mechanism

Glioblastoma is one of the most destructive and difficult malignancies to cure. It is distinguished by a 12-to-18-month life expectancy after diagnosis. Getting over the BBB to treat brain illnesses remains a major difficulty. While substantial advancements in delivery have been made on a variety of fronts, other areas still require additional research. The BBB is primarily consisting of endothelial cells present in the brain that line the capillaries and is the most appealing way to deliver substances into the brain because it presents fewer difficulties than direct delivery to the brain. These endothelial cells are connected by networks of tight junction although accompanied by glia (such as astrocytes and microglia), neurons, together with pericytes to create a neurovascular unit. The BBB, which keeps medications from spreading towards the tumour, makes it difficult for chemotherapy to reach the tumour, and radiotherapy's limitations make it difficult to eliminate radio-resistant GBM cells, particularly stem cells, all of which contribute to the ineffectiveness of standard treatments for glioblastoma multiforme (GBM).[24]Nps traps or dissolves the active ingredient (drug or biologically active substance), which are macromolecular solid colloidal particles with sizes ranging from 1 to 1000 nm (1 mm). Nps are unique in that they can be used to administer drugs and genes, as well as for imaging, diagnosis, and treatment.[25]

Delivery of nanoparticles to glioblastoma involves a complex interplay of various mechanisms that help the nanoparticles pass the BBB and penetrate the tumour tissue. Some of the key mechanisms at work include[26]:

Fig.1: Schematic illustration of Nanoparticles delivery system



Passive Targeting: Nanoparticles can diffuse passively into the tumour tissue due to the leaky vasculature of the tumour. The tumour vasculature has a larger inter-endothelial gap and lacks proper tight junctions that allow the particles to leak into the tumour tissue. Additionally, the tumour's abnormal lymphatic drainage is a factor in the retention of NPs. Small molecule medicines with near-instantaneous circulation and fast removal from the tumour, are exempt from this special feature. As a result, the incorporation of micro-molecule medications into nanosized drug delivery vehicles improves their pharmacokinetics (prolonged bioavailability), provides some tumour selectivity, and lessens adverse effects.[27] An acidic and hypoxic environment

characterises the glioblastoma microenvironment. These conditions can be made to make nanoparticles responsive, enabling their targeted accumulation in tumour tissue. For instance, acidic tumour microenvironment-responsive pH-sensitive nanoparticles can be created to release their cargo, enabling targeted drug delivery to glioblastoma cells.[28] Additionally, it is possible to create nanoparticles that react when certain proteins or enzymes are overexpressed in glioblastoma cells. For instance, peptide sequences that are specifically cleaved by matrix metalloproteinases (MMPs), which are overexpressed in glioblastoma cells, can be used to conjugate nanoparticles. This causes the nanoparticle cargo to be released only in the tumour tissue.[29]

Active Targeting: Nanoparticles can be programmed to target specific molecules found on cancer cells, including transferrin, epidermal growth factor receptors, as well as integrin receptors. This helps the nanoparticles to bind selectively to the tumour cells and get internalized. The use of ligands, such as antibodies or peptides, that selectively attach to receptors overexpressed upon the surfaces of glioma cells enables active nanoparticle targets in this illness. To facilitate their binding to tumour cells and improve their uptake, these ligands can be conjugated to nanoparticle surfaces.[30] Active targeting nanotechnology systems for drug delivery can overcome the limits of conventional medication therapy. The BBB is established in between neuroglia cells and cerebral capillaries. More than 98% of specific small molecules, such as chemotherapy drugs and other therapeutic molecules, are selectively restricted from paracellular diffusion via endothelial cell tight connections.[31] One example of active targeting in glioblastoma is the use of nanoparticles attached with transferrin, a protein that attaches to transferrin receptors overexpressed on the membrane of glioma cells. When chemotherapeutic drugs like temozolomide are loaded onto these nanoparticles and delivered to glioblastoma cells specifically, the antitumor effectiveness and systemic toxicity are improved.[32] Using nanoparticles conjugated with EGFR antibodies, which attach to EGFR overexpressed on the surface of glioma cells, is another example of active targeting. Small interfering RNA (siRNA) can be added to these nanoparticles to silence particular genes involved in tumour growth and invasion, leading to tumour regression and improved survival in preclinical studies.[33]

Receptor-mediated Transcytosis: In this mechanism, Endothelial cells take up the nanoparticles via specialised receptors and transfer them throughout the BBB to the malignant cells. The insulin receptor, a membrane glycoprotein found in both glioma cells and BCECs, is one illustration. Using PILs modified with 83-14 Murine Monoclonal Antibodies, an Antibody to the Human Insulin Receptor, the gene formulation could be guided to brain tumours in vivo.[34] The humanised 83-14 murine monoclonal antibody may be used in clinical treatments, according to numerous studies. The membrane-bound precursor of HB-EGF, also known as DTR, is another potential target location. CRM197, a non-toxic diphtheria toxin variant, was employed as a receptor-specific carrier protein that was connected directly to horseradish peroxidase in both BBB as well as neuroglial cells.[35][36]

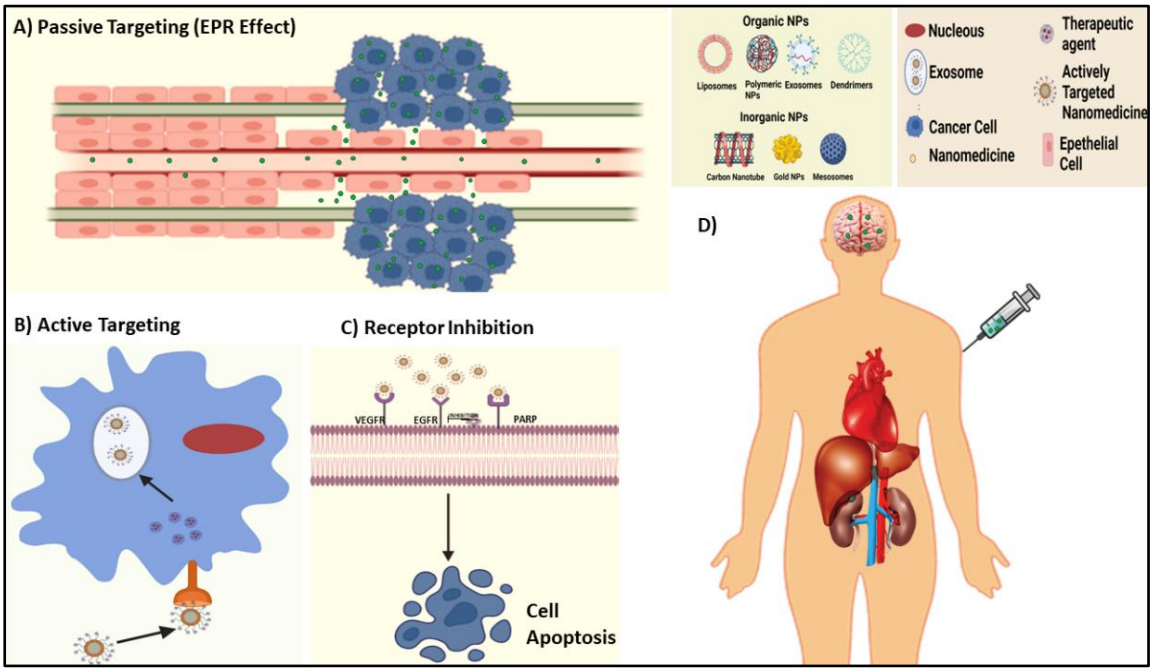


Fig.2 The passive targeting and active targeting of a tumour are depicted in this diagram.

Molecular markers associated with glioma:

MGMT:

In glioblastoma patients receiving chemotherapy with alkylating agents, the methylation condition of the MGMT promoter has been recognized as an important and self-reliant biomarker of survival. In glioblastoma, MGMT gene promoter methylation is without a doubt the genetic marker with the biggest impact on medical therapy. Secondary glioblastomas are more likely to have MGMT promoter methylation than primary glioblastomas (75% versus 36%).[40] The MGMT gene, which codes for a widely expressed enzyme that eliminates alkyl adducts from the O6 position of guanine, is found at chromosome 10q26.[37] Thymine and guanine are given an alkyl group by the drug temozolomide (TMZ), which damages DNA and starts the apoptotic process. A DNA damage repair protein called MGMT removes the guanine alkyl group and inhibits apoptosis.[38] The repair protein (MGMT; formerly known as alkyl guanine alkyltransferase6) encoded by the MGMT gene reverses this alkylation process. The MGMT protein receives a methyl moiety during this process, which causes it to be broken down and used. Epigenetic alteration of the CpG island at certain CpG sites within the promoter of MGMT silences the MGMT gene, resulting in poor repair of DNA alkylation and increased responsiveness to temozolomide.[39] The mismatch repair (MMR) system causes DNA double-strand breaks and permanent genome damage by removing the thymine but leaving the methylation guanine, resulting in cell death.[40]

1p and 19q chromosomal deletions:

A positive prognostic indicator for oligodendroglia tumours is 1p/19q codeletion (OT). Long recognised as a typical molecular hallmark of oligodendroglia tumours, There has been a simultaneous depletion of genetic information from chromosomal arms 1p and 19q.[41] The loss of one hybrid chromosome causes the LOH 3 in 1p and 19q. This molecular change is caused by an imbalanced whole-arm translocation between chromosomes 1 and 19 with the deletion of the derivative t(1p;19q), which occurs early in the pathogenesis of oligodendrogliomas. The biological impact of co-deletion of 1p/19q has been discussed. since 1994, but it is still not clear. 1p/19q co-deletion is a helpful prognostic, diagnostic, and predictive biomarker for oligodendroglia tumour therapy.[42][43]

Atrx:

Glioblastoma, the most common and fatal main brain tumour in humans mostly in adults, typically carries mutations in the ATRX gene (alpha thalassemia/mental retardation syndrome X-linked), which controls chromatin structure. Both grade 2/3 adult glioma and paediatric glioblastoma (GBM) which is H3F3A-mutant have recurrent mutations in the chromatin remodeler protein ATRX. The cell-cycle checkpoint regulatory gene CHEK1 and other genes associated with the cell-cycle phase transformation have regulatory elements that ATRX binds to, and Chk1 is downregulated in several rising gliomas (HGG) models when ATRX is lost. The ability of ATRX-deficient human and mouse GBM cells to maintain the G2/M cell-cycle checkpoint in response to radiation and targeted sensitization with ATM inhibition was also discovered to be reduced.[44] Alternative lengthening of telomeres, also known as telomere maintenance by non-telomerase methods, is strongly correlated with ATRX mutation (and loss of immune staining).[45]

EGFR/EGFRvIII:

Glioblastoma frequently amplifies the EGFR and its active variant EGFRvIII (GBM). Both EGFR and EGFRvIII play important roles in pathogenesis, patients have had poor results with EGFR-tyrosine kinase inhibitors (TKIs) or antibodies.[46] In order to treat cancer patients, the FDA has approved five anti-EGFR medications, Three small molecule antagonists and two antibodies were used. Gefitinib (ZD1839; Iressa), a small molecular weight EGFR kinase inhibitor, has been given approval for the treatment of locally advanced and metastatic non-small cell lung cancer, or NSCLC.[47] A humanised monoclonal antibody called cetuximab (C225; Erbitux interacts the both EGFR and EGFRvIII extracellular domains. It has been authorised for the treatment of head and neck squamous cell carcinoma that has spread or recurred after previous chemotherapy. As first-line therapy for advanced head and neck squamous cell carcinoma, it is additionally combined with radiation therapy. Cetuximab in conjunction with irinotecan is also approved for patients with metastatic colorectal cancer who have not responded to irinotecan alone and after other kinds of chemotherapy have failed.[48] An EGFR kinase inhibitor that is tiny in size called erlotinib (OSI-774; Tarceva) has been authorised for the treatment of metastatic NSCLC. Additionally, it has been given the go-ahead To be administered in conjunction with gemcitabine to treat pancreatic cancer that cannot be removed surgically or has spread.[49] A tiny chemical that targets both EGFR and Her-2 called lapatinib (GW572016; Tykerb/Tyverb) has been approved for use in combination in combination with other drugs to treat metastatic breast cancer. It is given to those with Her-2-positive positive cancer who have not reacted to prior treatments. [50] Panitumumab is a human monoclonal antibody that was created to target the extracellular domain of the EGFR (ABX-EGF; Vectibix). It has been approved for the treatment of colorectal cancer that has spread and has ended in failure previous therapies.[51]

Other biomarkers such as p53 tumour suppressor have a well-known role in cancer progression. Cell proliferation is limited by cellular stressors such as DNA damage, oncogenic activity, or hypoxia via p53-dependent cell cycle arrest in the G1 phase.[52] Even though glioma tissue expresses Platelet-derived growth factor-B(PDGF-B) and HIF1-alpha, which are closely linked to tumour angiogenesis and mediate vascular endothelial growth factor (VEGF) activity.[53] A driver tumour suppressor gene called CDKN2A controls cell cycle progression through the actions of the cyclin-dependent kinases CDK4 and CDK6. Loss of CDKN2A encourages the development of gliomas and tumour metastasis. Glioma classification and clinical outcomes are related to CDKN2A deletion.[54] The primary biochemical function of the phosphatidylinositol 3-kinases (PI3Ks), a family of lipid kinases, is to phosphorylate the 3-hydroxyl group of phosphoinositides. Glioblastoma multiforme frequently exhibits PTEN loss, which causes abnormal phosphoinositide 3-kinase pathway activation. Multiple protein kinases, including atypical protein kinase C, are activated as a result of

increased signalling through this pathway.[55] Mutations in isocitrate dehydrogenase 1/2 (IDH)1/2 are frequently found in gliomas. It is possible that IDH1 mutations develop after the development of a low-grade glioma and cause the tumour to advance to a glioblastoma.[56]

Novel Treatment Strategies for glioblastoma

Surgery

Glioblastoma is initially treated surgically. Establishing the diagnosis of glioblastoma requires tissue. It can be obtained through stereotactic, open, or tumour-specific microsurgery.[57] Surgery aims to remove as much of the tumour as feasible while causing the least amount of damage to healthy brain tissue. It is frequently impossible to completely remove the tumour, and after surgery, cancer cells may still be present.

Targeted therapy

Targeted therapy is a form of cancer treatment that targets specific chemicals that are required for cancer cell growth and survival. Contrary to early forecasts, phase II/III studies of targeted treatments in adult patients with glioblastoma have mainly failed. Recent studies have focused on improving patient classification, drug-tissue penetration, and target and adaptive pathway inhibition to maximise therapy response.[58] A targeted therapy drug called bevacizumab works to stop the development of new blood vessels in tumours, which may help to slow the growth of the tumour.[59]

Chemotherapy

Chemotherapy employs medication to eradicate cancer cells. Drugs for chemotherapy can be administered intravenously or orally. The standard of care for GBM now is chemotherapy using the drug temozolomide. The medicine is normally taken each day while receiving radiation therapy, and then for six cycles afterwards radiation, during the maintenance phase.[60]

Electric Field Therapy

Glioblastoma treatment using electric field therapy, also known as tumour-treating fields [TTfields], is relatively new. In cancer treatment, rod- or needle-like electrodes are carefully positioned in or around the desired lesion using electroporation variations, which are biophysical tissue ablation techniques. Due to its potential for invasiveness, electroporation is sometimes only possible with the surgical intervention.[61] Antimitotic processes are thought to be the main mechanisms of action by which TTFields application exerts its therapeutic effects. The reason why cancer cells are particularly sensitive to TTFields is that they divide more quickly than cells in healthy tissue. Furthermore, an examination of TTFields sensitivity in several types of cancer cells reveals an inverse association between TTFields-induced cell death and usual cell line doubling time. The precise frequency of the applied alternating electric fields also affects how well TTFields work.[62]

Immunotherapy

A form of cancer treatment known as immunotherapy aids the immune system of the body in recognising and destroying cancer cells. Cancer immunotherapy seeks to elicit a tumour-specific immune response capable of precisely eradicating cancer cells. This is performed by employing tumour-specific vaccines, dysregulated immunological checkpoints, or boosted autologous immunologic cells to manipulate the patient's immune system.[63] For the treatment of glioblastoma, immune checkpoint inhibitors like nivolumab and pembrolizumab are currently being researched.[64]

CAR T-cell therapy

CAR T-cell treatment is a type of immunotherapy that includes altering a patient's T-cells to recognise and kill cancer cells. CAR T cells are autologous or allogeneic-modified T cells isolated from a patient's peripheral blood, grown in vitro, and genetically transformed to produce CAR molecules on the cellular membrane by viral vectors or electroporation.[65]

Laser Interstitial Therapy (LITT)

In cases where GBM patients are not candidates for surgical debulking of the tumour via an open craniotomy, a relatively new procedure known as LITT is being tested as a potential cytoreductive technique in destroying tumour cells via a localised elevated temperature.[66]

Radiotherapy

Whole-brain radiation therapy has historically been applied. However, the current practice uses focal radiotherapy as a treatment because of the adverse consequences of radiation on the functional brain, such as cognitive impairment.[66]With adjuvant temozolomide, the 60 Gy total radiotherapy dose is typically administered over 30 fractions of 2 Gy, allowing normal brain cells to grow around the tumour treatment region to rest in between treatments. An effort has been made to discover alternative radiotherapy-based techniques since radiation dosage increases has resulted in greater tissue damage and side effects with no discernible difference in survival.[67][68]

Future Prospects

Glioblastoma is an aggressive form of brain cancer, and nanotechnology has the potential to completely alter how it is treated. Here are some potential applications of nanotechnology in glioblastoma in the future.

1. Personalized Medicine: Finding out which type of cell gave rise to the cancer is the first step in tailoring care for a patient with a brain tumour because the brain is made up of various sorts of cells. "Mixed" gliomas appear to develop from multiple cell types simultaneously, but most cases can be categorised as having started with an oligodendrocyte or an astrocyte (astrocytomas) (oligodendrogliomas). Personalised medicine makes use of information that is unique to each patient to improve therapeutic care. The most appropriate molecular target for the most successful treatment to address the patient's requirement will be identified using complete genomic, proteomic, transcriptomic, epigenomic, and other comprehensive patient profiles.[69]
2. Improved drug delivery: The BBB, which can prevent drugs from reaching the brain, can be bypassed by using nanoparticles to carry medications directly to the tumour site. Targeted delivery may reduce negative effects of chemotherapy medications while increasing their effectiveness. The development of nanoparticles with improved tumour targeting and drug release capabilities may be the main focus of future research.[70]
3. Multi-Modal Therapies: A variety of drugs or therapeutic agents can be carried by nanoparticles, enabling a combination of treatments. This strategy might help treat glioblastoma more effectively and overcome the resistance to single-drug therapies.
4. Imaging: For imaging procedures like magnetic MRI and computed tomography (CT) scans, nanoparticles can be used as contrast agents. This can aid medical professionals in better tumour visualisation and treatment response monitoring.[71] T1-weighted (T1w) and contrast-enhanced (T1CE), T2-weighted (T2w), and T2-fluid-attenuated inversion recovery (T2-FLAIR) sequences may be obtained with any clinical scanner and give crucial clinical information regarding a variety of processes in the tumour environment. In the past ten years, advanced MRI modalities have been used more frequently to characterise glioblastomas in greater detail. These include dynamic contrast enhancement (DCE), dynamic susceptibility contrast (DSC), higher-order diffusion techniques like diffusion tensor imaging (DTI), and MR spectroscopy (MRS). It takes a lot of effort to integrate these cutting-edge imaging modalities into improved clinical procedures and personalised treatment strategies. To reduce postsurgical neuro-deficits, eloquent cortices and significant tracts are being identified using functional MRI (fMRI) and tractography.[72]
5. Non-invasive therapies: Nanoparticles can be used in non-invasive cancer treatments like magnetic hyperthermia and photothermal therapy, which use heat to kill cancer cells. These treatments might provide a less harmful and invasive option to radiation therapy and conventional surgery.[73]

Conclusion:

The highly lethal and aggressive form of brain cancer known as glioblastoma is amenable to treatment with targeted nanotechnology. The blood-brain barrier can be bypassed and chemotherapy side effects can be reduced by using nanoparticles that are specifically designed to target the tumour site. They can also be utilised in non-invasive cancer treatments like magnetic hyperthermia and photothermal therapy, which use heat to kill cancer cells. Additionally, nanoparticles can be made to carry a variety of medications or therapeutic agents, enabling the combination of treatments. Future glioblastoma nanotechnology research may enhance drug delivery and create individualised medicine targeting particular tumour markers. The use of nanoparticles in diagnostics offers the possibility of early glioblastoma detection and diagnosis. Overall, glioblastoma personalised medicine strategies show great promise for enhancing patient outcomes in this aggressive cancer type. To fully comprehend the intricate biology of glioblastoma and to create efficient, individualised treatment plans, however, a great deal more study is required.

Abbreviation

GBM: Glioblastoma Multiforme

NPs: Nanoparticles

BBB: Blood-brain barrier

PLGA: poly lactic-co-glycolic acid

AgNPs: Silver Nanoparticles

CHEK 1: Checkpoint Kinase 1

CpG: cytosine phosphate-guanine

LOH: loss of heterozygosity

PILs: PEGylated immunoliposomes

HB-EGF: heparin-binding epidermal growth factor

DTR: Diphtheria toxin receptor

MGMT: O (6)-Methylguanine-DNA-methyltransferase

ZnONPs: Zinc oxide nanoparticles

ROS: Reactive oxygen species

EGFR: epidermal growth factor receptor

CT: computed tomography

MRI: Magnetic resonance imaging

References:

[1]. I. Khan et al., "Nanomedicine for glioblastoma: Progress and future prospects," Semin. Cancer Biol., vol. 86, no. Pt 2, pp. 172–186, Nov. 2022, doi: 10.1016/J.SEMCANCER.2022.06.007.

[2]. J. S. Michael, B.-S. Lee, M. Zhang, and J. S. Yu, "Nanotechnology for Treatment of Glioblastoma Multiforme," J. Transl. Intern. Med., vol. 6, no. 3, pp. 128–133, Oct. 2018, doi: 10.2478/JTIM-2018-0025.

[3]. M. E. Davis, "Glioblastoma: Overview of Disease and Treatment," Clin. J. Oncol. Nurs., vol. 20, no. 5 Suppl, pp. 1–8, Oct. 2016, doi: 10.1188/16.CJON.S1.2-8.

[4]. A. Cikankowitz, D. Se, and E. Garcion, "Nanomedicine to overcome radioresistance in glioblastoma stem-like cells and surviving clones," pp. 1–17, 2015, doi: 10.1016/j.tips.2015.02.002.

[5]. V. Venkataramani et al., "Glioblastoma hijacks neuronal mechanisms for brain invasion," Cell, vol. 185, no. 16, pp. 2899-2917.e31, Aug. 2022, doi: 10.1016/J.CELL.2022.06.054.

[6]. J. H. Kang and A. Desjardins, "Convection-enhanced delivery for high-grade glioma," Neuro-oncology Pract., vol. 9, no. 1, pp. 24–34, Feb. 2021, doi: 10.1093/NOP/NPAB065.

[7]. F. Zhang, C. L. Xu, and C. M. Liu, "Drug delivery strategies to enhance the permeability of the blood-brain barrier for treatment of glioma," Drug Des. Devel. Ther., vol. 9, pp. 2089–2100, Apr. 2015, doi: 10.2147/DDDT.S79592.

[8]. S. Ostrovsky, G. Kazimirsky, A. Gedanken, and C. Brodie, "Selective cytotoxic effect of ZnO nanoparticles on glioma cells," Nano Res., vol. 2, no. 11, pp. 882–890, Nov. 2009, doi: 10.1007/S12274-009-9089-5/METRICS.

[9]. Z. H. Marfavi, M. Farhadi, S. B. Jameie, M. Zahmatkeshan, V. Pirhajati, and M. Jameie, "Glioblastoma U-87MG tumour cells suppressed by ZnO folic acid-conjugated nanoparticles: an in vitro study," Artif. cells, nanomedicine, Biotechnol., vol. 47, no. 1, pp. 2783–2790, Dec. 2019, doi: 10.1080/21691401.2019.1577889.

[10]. J. S. Ananta, R. Paulmurugan, and T. F. Massoud, "Temozolomide-loaded PLGA nanoparticles to treat glioblastoma cells: A biophysical and cell culture evaluation," Neurol. Res., vol. 38, no. 1, pp. 51–59, 2016, doi: 10.1080/01616412.2015.1133025.

[11]. F. Madani, S. S. Esnaashari, T. J. Webster, M. Khosravani, and M. Adabi, "Polymeric nanoparticles for drug delivery in glioblastoma: State of the art and future perspectives," J. Control. Release, vol. 349, pp. 649–661, Sep. 2022, doi: 10.1016/J.JCONREL.2022.07.023.

[12]. P. V. AshaRani, M. P. Hande, and S. Valiyaveettil, "Anti-proliferative activity of silver nanoparticles," BMC Cell Biol., vol. 10, p. 65, Sep. 2009, doi: 10.1186/1471-2121-10-65.

[13]. M. Eugenio et al., "Silver/silver chloride nanoparticles inhibit the proliferation of human glioblastoma cells," Cytotechnology, vol. 70, no. 6, pp. 1607–1618, Dec. 2018, doi: 10.1007/S10616-018-0253-1.

[14]. G. Perini et al., "Graphene Quantum Dots' Surface Chemistry Modulates the Sensitivity of Glioblastoma Cells to Chemotherapeutics," Int. J. Mol. Sci., vol. 21, no. 17, pp. 1–17, Sep. 2020, doi: 10.3390/IJMS21176301.

[15]. D. Dhar, S. Ghosh, S. Das, and J. Chatterjee, "A review of recent advances in magnetic nanoparticle-based theranostics of glioblastoma," Nanomedicine (Lond)., vol. 17, no. 2, pp. 107–132, Jan. 2022, doi: 10.2217/NNM-2021-0348.

[16]. S. Wang et al., "Macrophage-Mediated Porous Magnetic Nanoparticles for Multimodal Imaging and Postoperative Photothermal Therapy of Gliomas," ACS Appl. Mater. Interfaces, vol. 13, no. 48, pp. 56825–56837, Dec. 2021, doi: 10.1021/ACSAMI.1C12406.

[17]. A. Mondal, D. K. Singh, S. Panda, and A. Shiras, "Extracellular Vesicles As Modulators of Tumor Microenvironment and Disease Progression in Glioma," Front. Oncol., vol. 7, no. JUL, Jul. 2017, doi: 10.3389/FONC.2017.00144.

[18]. F. Hanif, K. Muzaffar, K. Perveen, S. M. Malhi, and S. U. Simjee, "Glioblastoma Multiforme: A Review of its Epidemiology and Pathogenesis through Clinical Presentation and Treatment," Asian Pac. J. Cancer Prev., vol. 18, no. 1, p. 3, 2017, doi: 10.22034/APJCP.2017.18.1.3.

[19]. D. Friedmann-Morvinski, "Glioblastoma heterogeneity and cancer cell plasticity," Crit. Rev. Oncog., vol. 19, no. 5, pp. 327–336, 2014, doi: 10.1615/CRITREVONCOG.2014011777.

[20]. A. P. Becker, B. E. Sells, S. Jaharul Haque, and A. Chakravarti, "Tumor Heterogeneity in Glioblastomas: From Light Microscopy to Molecular Pathology," Cancers (Basel)., vol. 13, no. 4, pp. 1–25, Feb. 2021, doi: 10.3390/CANCERS13040761.

[21]. L. Oliver, L. Lalier, C. Salaud, D. Heymann, P. F. Cartron, and F. M. Vallette, "Drug resistance in glioblastoma: are persisters the key to therapy?," Cancer drug Resist. (Alhambra, Calif.), vol. 3, no. 3, pp. 287–301, 2020, doi: 10.20517/CDR.2020.29.

[22]. A. Ou, W. K. Alfred Yung, and N. Majd, "Molecular Mechanisms of Treatment Resistance in Glioblastoma," Int. J. Mol. Sci., vol. 22, no. 1, pp. 1–24, Jan. 2020, doi: 10.3390/IJMS22010351.

[23]. A. Vollmann-Zwerenz, V. Leidgens, G. Feliciello, C. A. Klein, and P. Hau, "Tumor Cell Invasion in Glioblastoma," Int. J. Mol. Sci., vol. 21, no. 6, Mar. 2020, doi: 10.3390/IJMS21061932.

[24]. E. Alphandéry, "Nano-Therapies for Glioblastoma Treatment," Cancers (Basel)., vol. 12, no. 1, Jan. 2020, doi: 10.3390/CANCERS12010242.

[25]. F. Pourgholi, M. hajivalili, J. N. Farhad, H. S. Kafil, and M. Yousefi, "Nanoparticles: Novel vehicles in treatment of Glioblastoma," Biomed. Pharmacother., vol. 77, pp. 98–107, Feb. 2016, doi: 10.1016/J.BIOPHA.2015.12.014.

[26]. M. Nowak, M. E. Helgeson, and S. Mitragotri, "Delivery of Nanoparticles and Macromolecules across the Blood–Brain Barrier," Adv. Ther., vol. 3, no. 1, p. 1900073, Jan. 2020, doi: 10.1002/ADTP.201900073.

[27]. M. F. Attia, N. Anton, J. Wallyn, Z. Omran, and T. F. Vandamme, "An overview of active and passive targeting strategies to improve the nanocarriers efficiency to tumour sites," J. Pharm. Pharmacol., vol. 71, no. 8, pp. 1185–1198, Aug. 2019, doi: 10.1111/JPHP.13098.

[28]. C. He et al., "LRP1-mediated pH-sensitive polymersomes facilitate combination therapy of glioblastoma in vitro and in vivo," J. Nanobiotechnology, vol. 19, no. 1, Dec. 2021, doi: 10.1186/S12951-020-00751-X.

[29]. A. Quesnel, G. S. Karagiannis, and P. S. Filippou, "Extracellular proteolysis in glioblastoma progression and therapeutics," Biochim. Biophys. acta. Rev. cancer, vol. 1874, no. 2, Dec. 2020, doi: 10.1016/J.BBCAN.2020.188428.

[30]. R. Razpotnik, N. Novak, V. CurinŠerbec, and U. Rajcevic, "Targeting Malignant Brain Tumors with Antibodies," Front. Immunol., vol. 8, no. SEP, Sep. 2017, doi: 10.3389/FIMMU.2017.01181.

[31]. Z. Liu, X. Ji, D. He, R. Zhang, Q. Liu, and T. Xin, "Nanoscale Drug Delivery Systems in Glioblastoma," Nanoscale Res. Lett., vol. 17, no. 1, 2022, doi: 10.1186/S11671-022-03668-6.

[32]. M. Porru et al., "Medical treatment of orthotopic glioblastoma with transferrin-conjugated nanoparticles encapsulating zoledronic acid," Oncotarget, vol. 5, no. 21, pp. 10446–10459, 2014, doi: 10.18632/ONCOTARGET.2182.

[33]. Y. Zou et al., "Single siRNA Nanocapsules for Effective siRNA Brain Delivery and Glioblastoma Treatment," Adv. Mater., vol. 32, no. 24, Jun. 2020, doi: 10.1002/ADMA.202000416.

[34]. Y. Zhang, H. J. Lee, R. J. Boado, and W. M. Pardridge, "Receptor-mediated delivery of an antisense gene to human brain cancer cells," J. Gene Med., vol. 4, no. 2, pp. 183–194, Mar. 2002, doi: 10.1002/JGM.255.

[35]. S. Wang, Y. Meng, C. Li, M. Qian, and R. Huang, "Receptor-Mediated Drug Delivery Systems Targeting to Glioma," Nanomater. (Basel, Switzerland), vol. 6, no. 1, Dec. 2015, doi: 10.3390/NANO6010003.

[36]. Y. C. Kuo and Y. C. Liu, "Cardiolipin-incorporated liposomes with surface CRM197 for enhancing neuronal survival against neurotoxicity," Int. J. Pharm., vol. 473, no. 1–2, pp. 334–344, Oct. 2014, doi: 10.1016/J.IJPHARM.2014.07.003.

[37]. N. Thon, S. Kreth, and F. W. Kreth, "Personalized treatment strategies in glioblastoma: MGMT promoter methylation status," Onco. Targets. Ther., vol. 6, pp. 1363–1372, 2013, doi: 10.2147/OTT.S50208.

[38]. K. Ludwig and H. I. Kornblum, "Molecular markers in glioma," J. Neurooncol., vol. 134, no. 3, pp. 505–512, Sep. 2017, doi: 10.1007/S11060-017-2379-Y.

[39]. A. Mansouri et al., "MGMT promoter methylation status testing to guide therapy for glioblastoma: refining the approach based on emerging evidence and current challenges," Neuro. Oncol., vol. 21, no. 2, pp. 167–178, Feb. 2019, doi: 10.1093/NEUONC/NOY132.

[40]. N. Senhaji, A. S. Houssaini, S. Lamrabet, S. Louati, and S. Bennis, "Molecular and Circulating Biomarkers in Patients with Glioblastoma," Int. J. Mol. Sci., vol. 23, no. 13, Jul. 2022, doi: 10.3390/IJMS23137474.

[41]. T. Siegal, "Clinical impact of molecular biomarkers in gliomas," J. Clin. Neurosci., vol. 22, no. 3, pp. 437–444, Mar. 2015, doi: 10.1016/J.JOCN.2014.10.004.

[42]. Q. T. Ostrom et al., "The epidemiology of glioma in adults: a 'state of the science' review," Neuro. Oncol., vol. 16, no. 7, pp. 896–913, 2014, doi: 10.1093/NEUONC/NOU087.

[43]. A. Idbaih et al., "Two types of chromosome 1p losses with opposite significance in gliomas," Ann. Neurol., vol. 58, no. 3, pp. 483–487, Sep. 2005, doi: 10.1002/ANA.20607.

[44]. T. Qin et al., "ATRX loss in glioma results in dysregulation of cell-cycle phase transition and ATM inhibitor radio-sensitization," Cell Rep., vol. 38, no. 2, Jan. 2022, doi: 10.1016/J.CELREP.2021.110216.

[45]. C. Koschmann, P. R. Lowenstein, and M. G. Castro, "ATRX mutations and glioblastoma: Impaired DNA damage repair, alternative lengthening of telomeres, and genetic instability," Mol. Cell. Oncol., vol. 3, no. 3, May 2016, doi: 10.1080/23723556.2016.1167158.

[46]. Z. An, O. Aksoy, T. Zheng, Q. W. Fan, and W. A. Weiss, "Epidermal growth factor receptor and EGFRvIII in glioblastoma: signaling pathways and targeted therapies," Oncogene, vol. 37, no. 12, pp. 1561–1575, Mar. 2018, doi: 10.1038/S41388-017-0045-7.

[47]. E. C. Da Silva et al., "Role of Endocytosis Proteins in Gefitinib-Mediated EGFR Internalisation in Glioma Cells," Cells, vol. 10, no. 11, Nov. 2021, doi: 10.3390/CELLS10113258.

[48]. M. Kaluzova, A. Bouras, R. Machaidze, and C. G. Hadjipanayis, "Targeted therapy of glioblastoma stem-like cells and tumor non-stem cells using cetuximab-conjugated iron-oxide nanoparticles," Oncotarget, vol. 6, no. 11, pp. 8788–8806, 2015, doi: 10.18632/ONCOTARGET.3554.

[49]. J. J. Raizer et al., "A phase II trial of erlotinib in patients with recurrent malignant gliomas and nonprogressive glioblastoma multiforme postradiation therapy," Neuro. Oncol., vol. 12, no. 1, pp. 95–103, Jan. 2010, doi: 10.1093/NEUONC/NOP015.

[50]. D. Patel et al., "Monoclonal Antibody Cetuximab Binds to and Down-regulates Constitutively Activated Epidermal Growth Factor Receptor vIII on the Cell Surface," Anticancer Res., vol. 27, no. 5A, pp. 3355–3366, Sep. 2007, Accessed: Mar. 29, 2023. [Online]. Available: https://ar.iiarjournals.org/content/27/5A/3355

[51]. F. Rivera, M. E. Vega-Villegas, M. F. Lopez-Brea, and R. Marquez, "Current situation of Panitumumab, Matuzumab, Nimotuzumab and Zalutumumab," Acta Oncol., vol. 47, no. 1, pp. 9–19, 2008, doi: 10.1080/02841860701704724.

[52]. Y. Jin, W. Xiao, T. Song, G. Feng, and Z. Dai, "Expression and Prognostic Significance of p53 in Glioma Patients: A Meta-analysis," Neurochem. Res., vol. 41, no. 7, pp. 1723–1731, Jul. 2016, doi: 10.1007/S11064-016-1888-Y.

[53]. D. Yoshida, K. Kim, M. Noha, and A. Teramoto, "Hypoxia inducible factor 1-alpha regulates of platelet derived growth factor-B in human glioblastoma cells," J. Neurooncol., vol. 76, no. 1, pp. 13–21, Jan. 2006, doi: 10.1007/S11060-005-3279-0.

[54]. H. Wang, X. Wang, L. Xu, J. Zhang, and H. Cao, "Analysis of the EGFR Amplification and CDKN2A Deletion Regulated Transcriptomic Signatures Reveals the Prognostic Significance of SPATS2L in Patients With Glioma," Front. Oncol., vol. 11, Apr. 2021, doi: 10.3389/FONC.2021.551160.

[55]. B. Markman, F. Atzori, J. Pérez-García, J. Tabernero, and J. Baselga, "Status of PI3K inhibition and biomarker development in cancer therapeutics," Ann. Oncol. Off. J. Eur. Soc. Med. Oncol., vol. 21, no. 4, pp. 683–691, Aug. 2010, doi: 10.1093/ANNONC/MDP347.

[56]. H. Yan et al., "IDH1 and IDH2 mutations in gliomas," N. Engl. J. Med., vol. 360, no. 8, pp. 765–773, Feb. 2009, doi: 10.1056/NEJMOA0808710.

[57]. H. G. Wirsching, E. Galanis, and M. Weller, "Glioblastoma," Handb. Clin. Neurol., vol. 134, pp. 381–397, 2016, doi: 10.1016/B978-0-12-802997-8.00023-2.

[58]. D. F. Chuang and X. Lin, "Targeted Therapies for the Treatment of Glioblastoma in Adults," Curr. Oncol. Rep., vol. 21, no. 7, Jul. 2019, doi: 10.1007/S11912-019-0807-1.

[59]. A. C. Tan, D. M. Ashley, G. Y. López, M. Malinzak, H. S. Friedman, and M. Khasraw, "Management of glioblastoma: State of the art and future directions," CA. Cancer J. Clin., vol. 70, no. 4, pp. 299–312, Jul. 2020, doi: 10.3322/CAAC.21613.

[60]. S. Jiapaer, T. Furuta, S. Tanaka, T. Kitabayashi, and M. Nakada, "Potential Strategies Overcoming the Temozolomide Resistance for Glioblastoma," Neurol. Med. Chir. (Tokyo)., vol. 58, no. 10, pp. 405–421, 2018, doi: 10.2176/NMC.RA.2018-0141.

[61]. E. P. W. Jenkins, A. Finch, M. Gerigk, I. F. Triantis, C. Watts, and G. G. Malliaras, "Electrotherapies for Glioblastoma," Adv. Sci. (Weinheim, Baden-Wurttemberg, Ger., vol. 8, no. 18, Sep. 2021, doi: 10.1002/ADVS.202100978.

[62]. O. Rominiyi, A. Vanderlinden, S. J. Clenton, C. Bridgewater, Y. Al-Tamimi, and S. J. Collis, "Tumour treating fields therapy for glioblastoma: current advances and future directions," Br. J. Cancer, vol. 124, no. 4, pp. 697–709, Feb. 2021, doi: 10.1038/S41416-020-01136-5.

[63]. J. A. Wilcox, R. Ramakrishna, and R. Magge, "Immunotherapy in Glioblastoma," World Neurosurg., vol. 116, pp. 518–528, Aug. 2018, doi: 10.1016/J.WNEU.2018.04.020.

[64]. U. Sener, M. W. Ruff, and J. L. Campian, "Immunotherapy in Glioblastoma: Current Approaches and Future Perspectives," Int. J. Mol. Sci., vol. 23, no. 13, Jul. 2022, doi: 10.3390/IJMS23137046.

[65]. L. Li et al., "Chimeric Antigen Receptor T-Cell Therapy in Glioblastoma: Current and Future," Front. Immunol., vol. 11, Nov. 2020, doi: 10.3389/FIMMU.2020.594271.

[66]. S. S. Stylli, "Novel Treatment Strategies for Glioblastoma," Cancers (Basel)., vol. 12, no. 10, pp. 1–11, Oct. 2020, doi: 10.3390/CANCERS12102883.

[67]. R. Stupp et al., "Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma," N. Engl. J. Med., vol. 352, no. 10, pp. 987–996, Mar. 2005, doi: 10.1056/NEJMOA043330.

[68]. I. J. Barani and D. A. Larson, "Radiation therapy of glioblastoma," Cancer Treat. Res., vol. 163, pp. 49–73, 2015, doi: 10.1007/978-3-319-12048-5_4.

[69]. Li, C. Di, A. K. Mattox, L. Wu, and D. C. Adamson, "The future role of personalized medicine in the treatment of glioblastoma multiforme," Pharmgenomics. Pers. Med., vol. 3, no. 1, pp. 111–127, 2010, doi: 10.2147/PGPM.S6852.

[70]. J. Li et al., "Nanoparticle Drug Delivery System for Glioma and Its Efficacy Improvement Strategies: A Comprehensive Review," Int. J. Nanomedicine, vol. 15, pp. 2563–2582, 2020, doi: 10.2147/IJN.S243223.

[71]. D. Chow, P. Chang, B. D. Weinberg, D. A. Bota, J. Grinband, and C. G. Filippi, "Imaging Genetic Heterogeneity in Glioblastoma and Other Glial Tumors: Review of Current Methods and Future Directions," AJR. Am. J. Roentgenol., vol. 210, no. 1, pp. 30–38, Jan. 2018, doi: 10.2214/AJR.17.18754.

[72]. G. Shukla et al., "Advanced magnetic resonance imaging in glioblastoma: a review," Chinese Clin. Oncol., vol. 6, no. 4, Aug. 2017, doi: 10.21037/CCO.2017.06.28.

[73]. M. Verduin et al., "Noninvasive Glioblastoma Testing: Multimodal Approach to Monitoring and Predicting Treatment Response," Dis. Markers, vol. 2018, 2018, doi: 10.1155/2018/2908609.