

Carmustine: Promising Drug for Treatment of Glioma

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ABSTRACT

Background: The treatment for glioma has challenging and survival rate is not more than one year after diagnosis. Carmustine is a non-specific antineoplastic agent that belongs to the nitrosourea group of compounds (bischlo-roethyl nitrosourea) and has various mechanisms of tumor cytotoxicity.

Main body: It can alkylate reactive sites on nucleoproteins as an alkylating agent, interfering with DNA and RNA synthesis and DNA repair. It can create interstrand crosslink's in DNA, preventing DNA replication and transcription. Under physiological conditions, carmustine undergoes spontaneous nonenzymatic decomposition, releasing reactive intermediates with alkylating and carbamoylating activities, which are thought to be responsible for carmustine's anticancer and cytotoxic properties. Human gliomas are the for the most part kind of tumor for brain. Gliomas can be treated with a variety of chemotherapeutics, but carmustine has recently emerged as a promising treatment option.

Conclusion: The adoption of a nose-to-brain medication delivery method has several advantages over efforts that try to breach the blood-brain barrier. The focused strategy also lowers the risk of cardiovascular harm. A significant advantage of nose to brain administration is the relatively high patient compliance. Research into new chemotherapeutic compounds and treatment delivery technologies is crucial for present and future patients

Keywords: Antineoplastic agent, Carmustine, Glioma, Nose-to-brain drug delivery, Olfactory receptor.

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INTRODUCTION

Cancer is the irregular expansion of cell. Normal cells divide and expand in a regulated manner to produce more cells as required to maintain body health. Cells die when they become old or destroyed, and are replaced by new ones. Cancer cells do not die; instead, they continue to expand and form new, abnormal cells. Normal cells are unable to invade (grow into) other tissues, whereas cancer cells can. A cell becomes a cancer cell when it grows out of control and invades other tissues. The extra cells may form a tumor, which is a mass of tissues. Tumors are classified as benign or malignant¹.

The aging and growth of the world population global burden of cancer continues to increase largely. After cardiovascular disorder maximum deaths occurs because of cancer in the world. Because of brain cancer in United State about 23,000 new cases and over 15,000 deaths in 2015 occur.² In India incidence around 2.5 million, with about 8, 00,000 new cases and 5, 50,000 deaths per annum.³ In India, the rate

of tumors in central nervous system (CNS) ranges from 5 to 10 per 100,000 people, with an upward trend.⁴

Benign tumors are actually can't showing characteristics like cancerous tumors. They are frequently removed and, in the majority of cases, do not reappear. Benign tumors could not multiply to further organs part of the body because their cells are not cancerous. Tumors that are malignant are cancerous. Tumor cells may invade surrounding tissues and spread to other parts of the body. The term "metastasis" refers to the multiplication of cells to further organs/parts of the body.¹

Cancer types can be classified into a few different categories.

The following are the most common types of cancer:

- **Carcinoma** is a type of cancer that starts in the skin or in the tissues that surround or line internal organs.
- **Adenocarcinoma** basal cell carcinoma, squamous cell carcinoma, and transitional cell carcinoma are some of the subtypes of carcinoma.

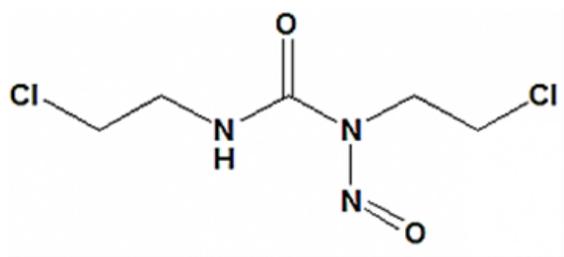


Figure 1: Structure of Carmustine.²⁹

- **Sarcoma** is a type of cancer that starts in the bone, cartilage, fat, muscle, blood vessels, or other connective or supportive tissues.
- **Leukemia** is a cancer that begins in blood-forming tissue, such as the bone marrow, and results in the production of large numbers of abnormal blood cells, which then enter the bloodstream.
- **Cancers of the central nervous system** begin in the tissues of the brain and spinal cord.¹

Brain and Central Nervous System (CNS) Cancer

A tumor in the brain is a mass of abnormal cells in the brain that has developed. The skull, which encases the brain, is extremely stiff. Any expansion in such a small space will cause problems. These tumors are abnormal cell growths occur from CNS. Primary brain tumors are tumors that start in the brain. A metastatic brain tumor is a cancer that starts in an extra part of the body and spreads to the brain. Brain tumors can be malignant (cancerous) or benign (non-cancerous) (benign). The pressure inside the skull can increase as benign or malignant tumors develop. This can result in brain damage, which can be fatal. Tumors of the CNS come in a variety of shapes and sizes. They develop in a variety of cell types and locations across spinal cord and brain. In children and adults, the types of tumor so as to develop and how they are treated. Anaplastic astrocytomas and glioblastomas account for about one-third of all brain tumors in adults. The most common type of brain tumor in children is astrocytomas. Although brain tumors rarely extend to extra parts of the body, they can spread through the brain tissue in most cases. Some of the symptoms of brain cancer include seizures, sleepiness, confusion, and behavioral changes.¹

The brain tumors are still idiopathic, but certain inherited or genetic conditions and exposure to extremely high radiation to head are risk factors. Surgery, radiotherapy, chemotherapy, or steroidal drugs, or a grouping of these treatments, may be used to treat brain tumors.

Major brain tumors are tumors that initiate in the brain. They may arise from brain cells, meninges, nerve cells, and glands.

Primary tumors may be cancerous or benign. Gliomas, also known as glioblastomas, and meningiomas, are the majority common types of brain tumors in adults.¹

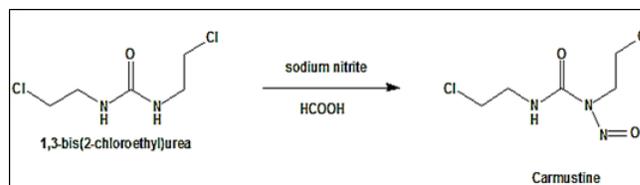


Figure 2: Synthesis of Carmustine.²⁹

Gliomas

These are tumors that originate from glial cells. These cells are responsible for supporting the structure of your CNS, providing nutrients to it, cleaning cellular waste, and breaking down dead neurons.

Gliomas may arise from a variety of glial cells. The following are examples of tumors which initiate from glial cells: astrocytic tumors, such as astrocytomas in the cerebrum, oligodendroglial tumors in the lobes, and glioblastomas from compassionate brain tissue, are the most aggressive.

Other Primary Brain Tumors

Primary brain tumors includes pineal gland tumors which can cause clinical symptoms such as vision changes and early puberty, key CNS lymphomas, which be malignant, primary germ cell tumors of the brain, which can be benign or malignant, meningiomas, which arise from the meninges, and schwannomas, which arise from cells that proliferate.

Secondary Brain Tumors

The majority of brain cancers are secondary brain tumors. They initiate from one location of body and multiply to the brain, which is called as metastasis. Secondary brain tumors are invariably cancerous. The following cancers have the potential to spread to the brain:

- Cancer of the lungs
- Breast cancer is a disease that affects women.
- Cancer of the kidneys
- Cancer of the skin⁵

Current Brain Tumor Therapies

Surgery, radiotherapy, chemotherapy, or steroidal drugs or a grouping of treatments may be used to treat brain tumors.

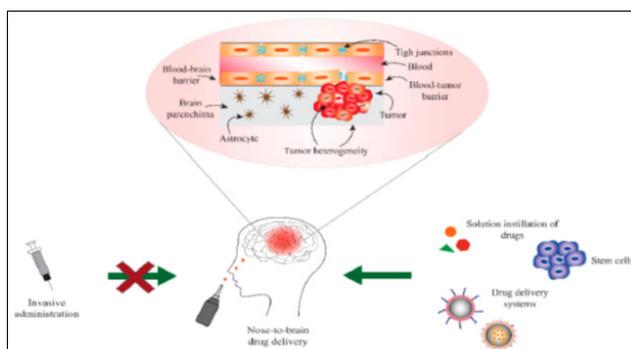


Figure 3: Obstacles and opportunities in the nose-to-brain drug delivery approaches for the treatment of Glioma.¹⁵

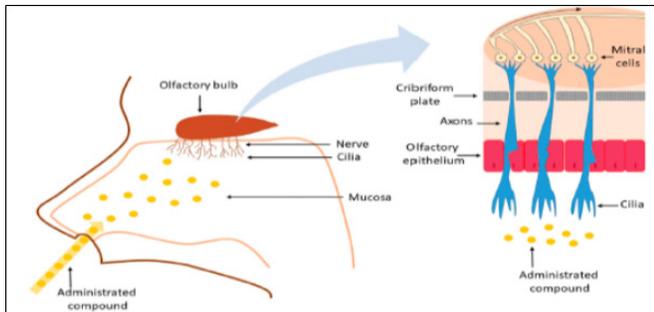


Figure 4: Structures involved in nose-to-brain transport by the olfactory pathway.¹⁵

Drugs for Brain Tumors

Brain tumor drugs that have been approved are as follows:

- Afinitor (Everolimus)
- Afinitor Disperz (Everolimus)
- Avastin (Bevacizumab)
- Bevacizumab
- BiCNU (Carmustine)
- Carmustine
- Carmustine Implant
- Everolimus
- Gliadel Wafer also called as a Carmustine Implant
- Lomustine
- Mvasi (Bevacizumab)
- Temodar (Temozolomide)
- Temozolomide
- Zirabev (Bevacizumab)⁶

carmustine (BCNU), lomustine (CCNU), temozolomide, vincristine and procarbazine, is the majority of successful drugs for brain tumor treatment so far.⁷

So, since carmustine is the first line of treatment for glioma, we'll go over it in depth here.

The nitrosourea compounds were discovered and developed as part of the NCI anticancer drug development program. The USFDA approved carmustine in March 1997 for the management of brain tumors, Hodgkin's disease and other lymphoma, and myeloma.⁸

MAIN BODY

Carmustine

Carmustine belongs to the alkylating agent category. Alkylating agents are most active when resting the phase of the cell. These drugs have no effect on the cycle of cell. The generic name of BiCNU® is carmustine (Figure 1).

Carmustine is an antineoplastic or cytotoxic chemotherapy drug. This is grouped as an alkylating agent. It is used to treat different brain tumors like glioblastoma, brainstem glioma, medulloblastoma, astrocytoma, ependymoma and metastatic brain tumors.

Chemical Formula: $C_5H_9C_{12}N_3O_2$

Molecular weight: 214.05 g/mol

Melting Point: 31°C

UV-Vis: λ_{max} : 231 nm

Half-life: 15–30 minutes

Storage Conditions: Carmustine powder must be refrigerated at 2 to 8°C. Both the powder and its solutions must be protected from light.

Appearance: A crystalline solid that ranges from off-white to yellow in color.

Solubility: Soluble in water (4 mg/mL) or 50% ethanol (150 mg/mL)

IUPAC Name: 1, 3-bis (2-chloroethyl)-3-nitrosourea

Synonyms

- BCNU
- bis-chloroethylnitrosourea
- Bischloroethyl nitrosourea
- Carmustine
- Carmustina
- Carmustinum
- N, N'-Bis (2-chloroethyl)-N-nitrosourea.

Structural Activity Relationship (SAR)

- Binding to the amino group increases the drug's oral route availability.
- The addition for substitute phenyl group can improve the drug's oral route availability.
- The addition of aromatic rings will improve the drug's stability.
- The aromatic ring will increase the drug's distribution throughout the body.
- The drug's general and onset of action can be provided by the benzimidazole ring.
- Benzimidazol will reduce the compound's half-life even more.

Method of Synthesis

Carmustine is made by nitrosing 1, 3-bis (2-chloroethyl) urea with sodium nitrite in an acidic, cold environment (Figure 2).

Pharmacodynamics

Carmustine is a nitrosourea that is used in the treatment of brain tumors, Hodgkin's disease, many myelomas, and non-Hodgkin's lymphomas. It is used as an individual or in combination treatment along another chemotherapeutic agent. Carmustine can't oppose with other alkylators, despite the fact that it alkylates DNA and RNA. By carbamoylation for amino acids in proteins, it, like other nitrosoureas, may inhibit several important enzymatic processes.

Bioavailability ranges from 5 to 28%.

Hepatic and rapid metabolism with active metabolites. Metabolites can stay in the bloodstream for days.

Route of Elimination

In 96 hours, approximately 60 to 70% of a total dose is excreted in the urine, with the remaining 10% passing through the lungs as CO_2 .²⁵⁻³¹

Carmustine's Mechanism of Action

Uncontrolled cell division, which is absent in normal tissue, is a hallmark of cancerous tumors. When "normal" cells come into contact with similar cells, a mechanism called contact inhibition causes them to stop dividing. This ability is lost in cancerous cells. The cell cycle is the mechanism by which cells divide, whether they are normal or cancerous. The cell cycle progresses from the resting to the active growing stages, and finally to mitosis (division).

Chemotherapy's ability to destroy cancer cells is dependent for stop cell division. The drugs usually destroy RNA or DNA by copying itself. The cells die when they can't divide. Chemotherapy is more likely to kill cells that can fast dividing, resulting in tumor shrinkage. Which mostly cause cell death (self-death or apoptosis). When cell are dividing then cell-cycle-specific chemotherapy drugs are affected. Cell-cycle non-specific chemotherapy drugs are those that affect cells while they are at rest. Chemotherapy is depending by different type of cells, their rate of division, and the time. Chemotherapy is usually given in cycles because of this. Chemotherapy is most effective in killing rapidly dividing cells. Chemotherapy, unfortunately, has no way of distinguishing between cancerous and common cells.

These "normal" cells can raise back and be strong, but side effects will occur in the meantime. The blood cells, cells in the stomach, mouth and bowel, and hair follicles are "normal" cells that are frequently affected by chemotherapy, thus decreasing blood counts, diarrhea, hair loss, mouth sores, and nausea. Carmustine belongs to the alkylating agent category. Alkylating agents are most active during the cell's resting phase. These drugs have no effect on the cell cycle. Alkylating agents come in a variety of forms.⁹

Carmustine was recently used as a drug for treating Glioma. However, due to side effects such as bone marrow suppression and pulmonary fibrosis, its use was limited.¹⁰ To limit its toxicity, currently, carmustine are available in the market in different dosage forms such as carmustine obivus 100 mg powder and solvent for concentrate for solution for infusion,¹¹ BiCNU (Carmustine) injection for intravenous use,¹² carmustine wafer (Gliadel® wafer),¹³ BCNU self-emulsifying implant.¹⁴ These gliadel wafers were not effective due to poor penetration, inability to prevent tumor recurrence, and lack of synergetic action with other chemotherapeutic drugs and/or radiotherapy.¹⁰ Different drug delivery systems have recently been developed to address these issues.

INTRANASAL ROUTE

Carmustine (BCNU) could be delivered to the brain via the intranasal route, which is non-invasive and bypasses the BBB (Figure 3).

In-vitro testing for checking ability of magnetic-targeted to brain using carmustine nano-com-plex was formulated out by Olufemi D. Akilo *et al.* in 2016. This work used polyvinyl alcohol/polyethyleneimine/fluorecein isothiocyanate complex (Polyplex) coated iron-oxide nanoparticles (magnetite) were

synthesized employing co-precipitation, epoxidation and EDC/NHS coupling reactions. TGA, NMR, XRD, TEM, and Zeta size analysis were used to characterize the nano-co-plex. The researchers discovered super paramagnetic hexagonally shaped "core-shell" nanoparticles with cell labeling properties, with sizes ranging from 30 to 50 nm and a zeta potential of +322 mV. The nano-co-plex synthesized was found to possess high degree of crystallinity with 32% polyplex coating. These analyses revealed that the loading capacity was time-dependent, with 176.82 g BCNU mg carrier. The cytotoxicity carmustine loaded formulation was shown superior to that of standard BCNU. In the presence of an external magnetic field, HG cells showed increased uptake and internalization of BCNU-loaded nano-co-plex. These nano-co-plexes may be perfect for BCNU delivery as an intranasal magnetic drug targeting device.¹⁶

In this study carmustine were taken in to the intranasal for nose-to-brain delivery of drug for targeting glioma. Hence, this research proved that carmustine is a suitable candidate for nose-to-brain drug delivery.

So it was concluded that nasal cavity has excellent location for drug delivery since the nasal mucosa has excellent absorption and permeability for both small molecule and biopharmaceutical drugs. In addition, roof for nasal cavity has very close to skull of brain base and consists nerves to brain. As a result, drug delivery from nose-to-brain has promising strategy for bypassing BBB and blood-cerebrospinal fluid barrier. Nose-to-brain delivery is a low-risk procedure with good patient compliance and the possibility of self-medication. The trigeminal and olfactory nerves are used to deliver drugs in to brain through the nose-to-brain drug route (Figure 4). Nose-to-brain delivery isn't limited to small molecule drugs; peptides and proteins, as well as stem cells, viruses, and nucleotides, have all been shown to pass through the nose and into the brain. Substance delivery from nose-to-brain will be a direct and minimally invasive way to target the site of action in cancer and other neurological disorders such as Alzheimer's and Parkinson's.¹⁷

Derek Fewer *et al.* 1972 reported chemotherapy of brain tumors clinical experience with carmustine (BCNU) and vincristine. Eighty-one patients having major/metastatic brain tumors be treated using [1, 3-Bis (2-chloroethyl)-1-nitrosourea] alone or carmustine and vincristine sulphate combined in that study and their responses were evaluated. A response was characterized as a significant clinical improvement that was not caused by corticosteroid therapy. Carmustine had a response rate of 48%, while the combination had a response rate of 30%. Glioblastoma patients had response rates of 53 and 25%, respectively. Ependymomas were the most responsive tumors, while metastatic tumors were the least responsive. Carmustine's dose-limiting toxicity was exclusively hematologic, while vincristine's was entirely neurologic, and both were serious enough to make determining drug effectiveness difficult. They found that carmustine is an effective with an appropriate level of toxicity based on the

final results. Because vincristine did not improve the efficacy of carmustine, they stopped using the two drugs together.¹⁸

Garside *et al.* 2007 made review on a carmustine implants and temozolomide were evaluated for their efficacy and cost-effectiveness in the treatment of newly diagnosed high-grade glioma. They included trials that were evaluated for key aspects of internal and external validity. Relevant information was gathered, and a narrative synthesis of the evidence was created. The model compared carmustine wafers (BCNU-W) and TMZ to current standard surgery and radiotherapy treatment. The simulated cohort was 55 years old on average and was modeled over a five-year period. Finally, the researchers concluded that BCNU-W does not provide a significant survival benefit to patients having grade-III tumors when compared to placebo. Patients with grade IV tumors do not seem to have a survival advantage. There has been no evidence of an increase in PFS. Limited evidence suggests that TMZ having important benefit in generally endurance. However, in grade IV tumors is unknown. The model's data was derived from limited evidence of varying quality. The type of tumor is clearly important when determining a patient's prognosis with various treatments. Grade IV tumors general types and appear to have the lowest chance of responding to treatment. Genetic and biomarkers may be used in the future to help identify subtypes that will react. More research into the efficacy of these drugs, as well as genetic markers, chemotherapy regimens, patient and caregiver quality of life, and patient perspectives on survival advantages vs. treatment disadvantages, is recommended.¹⁹

Hans Christoph Bock *et al.* 2010 studied a multicenter experience with carmustine implants and concomitant radiochemotherapy as first-line treatment for malignant glioma. Randomized diagnosed malignant glioma in phase-III clinical trials showed a substantial improvement in survival after implantation of 1, 3-bis (2-chloroethyl)-1-nitrosourea (carmustine) wafers at 1, 2, and 3 years. However, these studies. The diagnosed glioblastoma in 44 patients they seen at the postoperative clinical course, the prevalence and severity of adverse events, the progression-free interval, and overall survival. Tumor surgery, carmustine wafer, and concurrent radio chemotherapy were all used in all of the patients. Later than the middle of 15.6 months of summarize, 28 patients among glioblastoma who expected gliadel wafer at main operation had died, 16 patients (36%) be active, and 15 patients show no medical or radiographic development. Twenty-three patients (52%) had any kind of adverse event. Grade 3 or 4 adverse events have shown in 19 patients (43%). Cerebral edema, healing anomalies were among the surgical complications. Newly diagnosed seizures, changes in psychological condition, and original neurological deficit were with the CNS side effects. Formation of clot in blood vessels and hematotoxicity were medical complications. In aggressive multimodal treatment, schedules looks appealing and may take advantage of the sensitizing effect of TMZ and carmustine on MGMT and AGT on their respective drug resistance genes. Our findings show that the combination of chemotherapeutic

agents among concurrent radiotherapy consists a noteworthy threat of toxicity, which is currently underappreciated.²⁰

Lawrence Kleinberg *et al.* 2016 reported that randomized placebo-controlled trials, BICNU instill wafers be exposed toward add to endurance within patients undergoing a by total resection of recently diagnosed otherwise regular cruel glioma. Carmustine wafer treatment was approved in US and European countries depending on these trials. Adverse events are rare, and since this therapy is administered during operation, this couldn't consist the patient's overall treatment burden. Nonetheless, it appears that this treatment is underutilized. This article examines proof of the patient-friendly therapeutic ratio and potential roadblocks. These problems must be considered for optimum use of this therapeutic approach, and they may become more important as this technology and other local therapies advance in the future.²¹

Shufeng Yi *et al.* 2019 reported a new approach toward preparation of carmustine; bioactive nanoparticles in PLGA (poly (D, L-lactic-coglycolides) acid) biocomposite spheres for glioma therapy and nursing care human gliomas can good number general form of brain tumor. Gliomas can be treated with a variety of chemotherapeutics. They are, however, expensive and have various side effects. The creation of a nanocomposite based on a chemotherapeutic drug and a tinny nanoparticle consists by polymer can extremely beneficial in the fight against glioma. The effectiveness of carmustine consisting gold nanoparticles associated with PLGAPSPE as a bio-nanocomposite used for the treatment of glioma and burn wounds was studied in this study. Biophysical methods were used to characterize the synthesized biocomposite. The synthetic composite's hexagonal and crystalline character was observed. The particle had a good combustible property, according to TGA analysis. Surprisingly, Cm-Au-PLGA-PSPE complex have a strong anti-tumor effect in the U251 human glioma cell line. Flow cytometry showed that glioma cells showing for bio-nanocomposite had a higher rate of apoptosis (62.31%). In addition, treatment with the Cm-Au-PLGA-PSPE composite resulted in a higher drop into feasibility of U251 cells. Cm-Au-PLGA-PSPE composite therapy resulted in rapid healing of heart, liver, spleen, lung, and renal tissue wounds in mice. The newly developed Cm-Au-PLGA-PSPE composite, according to this study, would be a talented option for treatment of human gliomas with related wounds.¹⁰

Satapathy *et al.* 2020 reported the U87MG cell line; carmustine-loaded nanosize lipid vesicles exhibited preferential cytotoxicity and internalization and enhanced biopharmaceutical parameters in mice: The approach on behalf of glioma therapy. In that study, experimental NLVs (nanosize phospholipids vesicles) were created using a traditional lipid layer hydration technique and characterized using various *in-vitro* techniques such as diffraction light scattering (DLS), zeta potential, field emission scanning electron microscopy (FESEM), cryo-transmission electron microscopy (cryo-TEM), *in-vitro* drug loading capacity, and drug release studies. The final API-consisting nanosized lipid vesicles are tested *in-vitro*

for cytotoxicity and cellular uptake in the U87MG person glioblastoma cell line. Swiss albino mice were used in an *in-vivo* pharmacokinetic study. The average vesicle diameter was 92 nm, with a narrow size distribution, according to DLS statistics. According to FESEM data, optimized CNLVs (Carmustine loaded nanosize phospholipids vesicles) were spherical in shape with a smooth surface. The formation of unilamellar vesicles with intact outer bilayers was confirmed using cryo-TEM. For the optimized CNLVs, a fair drug loading of 7.8% was observed and a sustained release of CS over a 48 hour study period. In the U87MG cells, an outside body cytotoxicity analysis showed that CNLVs were significantly more toxic than free drugs. Confocal microscopy revealed that final API-consisting nanosize lipid vesicles be successfully internalized in the tested cell line. Pharmacokinetic data showed that optimized CNLVs had a longer mean residence time in the blood than free drug. Following further *in-vivo* testing, it was concluded that this study has the potential of experimental CNLVs used for treating to glioma.²²

Erthal *et al.* 2020 made review on glioblastoma multiforme can be treated with biocompatible copolymer formulations. They stated that treatment for glioblastoma multiforme (GBM) can still not change from 20 years, despite the prognosis for patients remains poor, with the majority of patients living less than a year after diagnosis. Original treatment for glioblastoma consisting surgery with radiotherapy and temozolomide-based oral chemotherapy. In cases of recurrent glioma, carmustine wafers are fixed into the brain after removing the tumor. There is a lot of research going on right now to improve GBM treatment outcomes and patient quality of life. Biomaterials are on the cutting edge of new treatment options exploration. Biocompatible polymers, in particular, have been suggested for use in hydrogel-based formulations. Chemotherapeutic API's, nano particles, nucleic acids, cells, and investigative substances are all examples of pharmacological agents that can be included in these formulations. They explain the novel formulations and tested *in-vitro* and *in-vivo* with unusual types of hydrogels in this manuscript. They developed formulation specially for treating GBM.²³

Zhi-Ze Xiao *et al.* 2020 reported a review on carmustine as a secondary treatment alternative for glioblastoma. They wrote in that review violent kind of primary malignant brain tumor is glioblastoma (GBM), also known as glioma. Gliomas, including GBMs, are treated with carmustine through intravenous injection or local implantation in the resection cavity. Carmustine's therapeutic potential, is underappreciated. Current research aimed to see if carmustine had any survival benefits in glioma patients, particularly those with GBM. They used techniques in that research. The Jadad and Newcastle–Ottawa scales were used to determine quality (NOS). The Revman 5.3 software was used to perform the statistical analysis. Twenty-two RCTs and cohort research with a total of 5,821 glioma patients were consisting in the findings. Overall, glioma persons consisting carmustine treatment shows a better progression-free survival (PFS; hazard ratio (HR) = 0.85 and

95 percent confidence interval (CI) = 0.77–0.94 and P = 0.002) and overall survival (OS; HR = 0.85, 95% CI = 0.79–0.92, P 0.0001) than those who did not. And lastly, those patients with a combination of carmustine and temozolomide therapy had a longer overall survival (HR = 0.78 and 95% CI = 0.63–0.97 and $p = 0.03$) than those who received TMZ alone. Finally, it was determined that carmustine implantation in the resection cavity improves GBM patient's survival, and it must important original treatment by providing a bridge between surgical resection and temozolomide therapy initiation.²⁴

CONCLUSIONS

In recent years, novel target-specific drugs with effective delivery strategies have characterized brain cancer treatment. The treatment of glioma is a great medical challenge due to both the disease aggressiveness and tumor location. However, the prognosis and median survival of personas consisting glioma are still unsatisfactory. It can be because of brain tumor molecular heterogeneity, the presence of cancer stem cells (CSCs), and the lack of efficient drug delivery because of present blood-brain-barrier. The use of nose to brain delivery mechanism in drug application has some advantages over strategies that aim to cross the blood-brain barrier. The targeted approach also reduces the chances for cardiovascular toxicity. The relatively high patient compliance is a significant benefit of nose to brain delivery. For current and future patients, research into new chemotherapeutic molecules as well as new methods of treatment administration is critical. Indeed, administering treatment locally consists with promising strategy for improving therapeutic outcomes. Components or transporter systems will be a viable strategy in the future. Combinatorial therapy is another potential future approach, in which tumor cells/CSCs may be easily targeted through BBB destruction/modification. This type of approach may be aided by modern methods such as nanotherapy. As a result, future research should focus on developing more precise targeting strategies to cure brain cancer while overcoming the challenges posed by the presence of the BBB.

LIST OF ABBREVIATIONS

CNS- Central Nervous System, NCI- National Cancer Institute's, TGA- Thermo gravimetric analysis, NMR- Nuclear Magnetic resonance, XRD-X-ray Diffractometry, TEM- Transmission Electron Microscopy, BBB- blood brain barrier, TMZ- Temozolomide,

DECLARATIONS

Availability of Data and Materials

Data sets generated during the current study are available from the corresponding author upon reasonable request.

CONFLICT OF INTERESTS

The authors declare that they have no competing interests.

AUTHOR CONTRIBUTIONS

Audumbar Mali designed the study, collected and interpreted the data and wrote the manuscript. Anil Bhanwase reviewed

the draft manuscript. All authors have read and approved the final manuscript.

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