Carmustine (Gliadel Wafers) for Fight against Brain Tumor: A Review

Syeda Khair-ul-Bariyah

Department of Chemistry, Forman Christian College (A Chartered University), Lahore, Pakistan

ABSTRACT

Among the various forms of brain tumor glioblastoma is an extremely fatal and rapidly growing form. Inspite of the conventional therapies including surgery, radiotherapy and chemotherapy, the survival rate is not much. Some drug delivery systems can cross the blood-brain barrier. Gliadel wafers (carmustine wafers) involve controlled release of the drug from biodegradable polymer wafers but the wafer provides an effective release of the anticancer 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) for only 5 days. It has been proposed that miR-221 regulated cell proliferation and BCNU develops resistance in glioma cells by targeting PI3-K/PTEN/Akt signaling axis which is a new therapy target for treatment of glioblastoma. The application of BCNU/VM26 in patients with later stages of recurrent GBM is not supported. For patients who undergo resection for symptomatic or large-volume metastasis or for tissue diagnosis, the addition of Gliadel wafers is a good option. The co-encapsulation of BCNU and BG into PLGA/CS NPs enhances the efficacy of BCNU. The combination CTX-NO suggests novel approaches to treat cancer. Inspite of all the progress, still some areas need study.

Keywords: Glioblastoma, Gliadel wafers, Carmustine, BCNU, glioma cells

INTRODUCTION

Intracranial neoplasm, which is commonly referred to as brain tumor, occurs due to abnormal growth of cells within brain. The two types of tumors are malignant tumors and benign tumors. The tumors starting from brain are primary in nature and brain metastasis spreads from some other sources. The common forms of primary tumors in adults are meningiomas and astrocytomas like glioblastomas. Medulloblastoma is the common type in children. Whatever the nature of tumor may be, the symptoms include headaches, seizures, vision issues, mental fatigue and vomiting. Difficulty in walking, speaking and inaccurate sensation may occur and as the disease progresses unconsciousness may result. The variation in the severity of the symptoms is due to size and location of tumor. There are a lot of factors responsible for tumor including inheritance like neurofibromatosis, Von Hippel-Lindau disease, multiple endocrine neoplasia and exposure to radiations i.e. ionizing radiations and chemicals like vinyl chloride\(^1\). Mutations and deletions of tumor suppressor genes like p53 are thought to be responsible for some brain tumor types\(^2\). The treatment of brain tumor can be either by surgery, radiation therapy, chemotherapy or a combination of all. Seizures may occur at times which are controlled by anticonvulsant medicines.

Chemotherapy

Chemotherapy is the destruction of cancer cells via cytotoxic (anti-cancer) drugs. This treatment technique is not much successful in the treatment of most of the brain tumor types as the blood-brain barrier hinders the drugs to reach cancer cells. It is used in cases where there is faster growing primary
brain tumor along with radiotherapy or in instances where the tumor has reoccurred. Shrinkage of
tumor and growth retardation are the sole benefits of chemotherapy in such states.

Chemotherapy Drugs

The chemotherapy drugs are given as tablets/capsules and some are given via injection intravenously. Implantation is also done during craniotomy to remove part or the entire tumor. They are called Gliadel implants and are small wafers or discs containing chemotherapy drug like carmustine. With the dissolution of the wafers, which are placed up to eight by surgeons, the drug is released in the blood. The chemotherapy drugs for the treatment of primary brain tumor are

- Temozolomide
- Lomustine
- Carmustine
- Vincristine
- Procarbazine

Carmustine

Carmustine, an orange yellow solid, is also known by the names bis-chloroethylnitrosourea, BCNU or BiCNU. It is used as a dialkylating agent in chemotherapy which forms interstrand cross links in DNA, thus, preventing DNA and RNA synthesis. Carmustine is used in the cure of various brain tumors like astrocytoma, glioma, glioblastoma medulloblastoma, multiforme, multiple myeloma, Hodgkin's disease and other lymphomas. It results in death of malignant cells. Carmustine is highly metabolized. Administration of the drug is intravenous (IV) with complete absorption. The drug is highly lipid soluble and penetrates CSF entering breast milk. The chemical and biologic half-life of carmustine is 5 min and 15-30 min, respectively.

The National Institute for Health and Clinical Excellence (NICE) suggests the use of Gliadels as treatment for newly diagnosed high-grade glioma, in case 90% or more of the tumor is removed. The structural formula of the drug is as follows

![Figure1. Chemical Structure of Carmustine (C₅H₇Cl₂N₂O₂)](image)

Everyone does not experience the side effects of the drug. The expected side effects of the drug are loss of appetite, tiredness, decrease in blood counts, weakness and nausea. Other side effect may also accompany like flushing of skin, pain or swelling at the injection site, difficulty breathing, pulmonary lung toxicity, loss or increase of weight and breath and menstrual issues. The long term effects include renal failure.

The aim of the present article is to focus on the success that carmustine and its derivatives have achieved from 2010-2015 in the treatment of all forms of brain tumor and to suggest some targets for future study.

EFFICACY OF CARMUSTINE IN BRAIN TUMOR
Carmustine has been reported to show efficacy in Glioblastoma multiforme (GBM) treatment. Biodegradable poly[(d,l)-lactide-co-glycolide] nanofibrous membranes facilitated release of carmustine (or bis-chloroethylnitrosourea, BCNU), irinotecan and cisplatin. Characterization of the in vivo and in vitro release behaviours of pharmaceuticals was carried out by an elution method and a high-performance liquid chromatography assay. Results indicated the release of high concentrations of BCNU, irinotecan and cisplatin for a period of more than 8 weeks in the cerebral cavity of rats and progressive atrophy of the brain tissues without inflammatory reactions was also investigated by histologic examination. Hence, biodegradable drug-eluting nanofibrous membranes were seen to facilitate sustained delivery of chemotherapeutic agents in the cerebral cavity, increasing the therapeutic efficacy of GBM treatment. Polymerically delivered carmustine (BCNU) wafers, when placed on the tumor-resection cavity surface, provided chemotherapeutic effects to residual tumor cells in times when delay was there between surgery and chemoradiotherapy. The polymeric wafers of carmustine were seen to be an effective salvage treatment following resection of a brain metastasis which failed prior SRS. After wafer implantation, those patients who showed successful local control, linear enhancement at the cavity was commonly observed.

Studies done in 2014

Once patients had progressed on a bevacizumab-containing regimen, then no treatments for recurrent glioblastoma were found. Adult patients with glioblastoma were detected and treated with carmustine or lomustine combined with bevacizumab as a second or third regimen after failing an alternative initial bevacizumab-containing regimen. For each treatment, response rate (RR), 6-month progression free survival (PFS6) and progression-free survival (PFS) were observed. The scheme did not prove to be of benefit for most patients. In one study, patients with recurrent GBM were treated with BCNU (130-150 mg/m², days 1/42) and VM26 (45-60 mg/m², days 1-3/42). They were analyzed for progression-free survival, overall survival and toxicity. Identification of fifteen patients of median age 52 years was done. Median progression-free survival was 2 months and median overall survival was 4 months. Hematotoxicity ¾ was developed by two patients (14%) and non-hematological toxicity≥ grade 3 was not seen. Application of BCNU/VM26 in late stages of recurrent GBM was not supported. In Chinese patients with recurrent malignant gliomas the safety of implants with 20 mg BCNU in each were evaluated. The implants were reported to be safe for patients. The potency of second surgery along with carmustine wafers and intravenous fotemustine was analyzed. This multimodal strategy was found to be feasible in patients with recurrent glioblastoma. In glioma cells, including BCNU-resistant cells, miR-221 was seen to be over-expressed and miR-221 regulated cell proliferation and BCNU resistance was also found. This over-expression led to cell survival and BCNU resistance and reduced cell apoptosis induced by BCNU. Knockdown of miR-221 inhibited cell proliferation and cell apoptosis and BCNU sensitivity was prompted. Down-regulation of PTEN and activation of Akt were also seen resulting in cell survival and BCNU resistance. A successful multicenter phase I/II study was carried out on Japanese patients suffering from malignant gliomas using Glaidel wafers having 8 sheets maximum and 61.6 mg BCNU. Study was carried out to determine whether intraoperative pathological diagnosis (IOD) using frozen section (FS) could differentiate high-grade glioma from WHO grade II gliomas. The sensitivity and specificity of IOD were 96.1% and 98.0%, respectively. In all glioma cases, the positive predictive value and the underestimation ratio of glioma grading were 51.5% and 43.5%, respectively. As per PS pathology, 54.5% of grade II glioma cases were in real grade III or IV. Recurrent cases and older age (>50 years old) were predictive factors resulting in underestimated grade II (FS) group (grade II ((FS))/III((PS))+IV((PS))). The temporary WHO grade by IOD as a result was underestimated in
almost half of glioma cases\textsuperscript{13}. The exploration of the role of Par-4 in drug-induced cytotoxicity was carried out using human glioma stem cell line-HNGC-2 and primary culture (G1). The panel of drugs used were lomustine, carmustine, UCN-01, oxaliplatin, temozolomide and tamoxifen (TAM) and only TAM induced cell death along with up-regulation of Par-4 levels\textsuperscript{14}. The characteristics of post-operative haemorrhage after carmustine wafer insertion were reported. Carmustine wafers were inserted in 177 patients in University Hospital of North Staffordshire and Wessex Neurological Centre, Southampton. In 4.4\% of the patients, site haematomas were observed. Acute operative site haematoma was seen in 0.81\% patients who went through resection without glial wafer insertion. The factors responsible for delayed post-operative haematoma were unclear\textsuperscript{15}. Tumor metastasis and progression is facilitated by cells acquiring morphologic and molecular alterations via a process called epithelial-to-mesenchymal transition (EMT). At present, chemoresistance has been thought of to be associated with EMT acquisition in cancer. The occurrence of the phenomenon in glioma is not certain. Human glioma cell lines SWOZ1, SWOZ2 and SWOZ2-BCNU were used to assess cellular morphology, molecular changes, migration and invasion. BCNU-resistant cells exhibited multiple drug resistance and phenotypic changes like spindle-shaped morphology and increased pseudopodia formation. Compared to SWOZ2 cells, lessened expression of the epithelial adhesion molecule E-cadherin and enhanced expression of the mesenchymal marker vimentin were investigated in BCNU-resistant SWOZ1 and SWOZ2-BCNU cells. The results showed a linkage between drug resistance and EMT induction in glioma cells\textsuperscript{16}.

Studies done in 2013

Treatment of malignant glioma in patients was reported to be done successfully by temozolomide (TMZ) and carmustine (BCNU) Gliadel wafers\textsuperscript{17}. Gliadel wafers were investigated to increase survival and local control in newly diagnosed GBM patients, but, there was high complication rate too, thus, making it ineffective for use in GBM\textsuperscript{18}. In one study, patients with brain metastases exhibited improvements in their cognitive trajectory after treatment with resection plus carmustine wafers (CW). The local control rate was 78\% comparable to rates of surgery with whole-brain radiation therapy (WBRT) and superior to WBRT alone\textsuperscript{19}.The co-encapsulation of carmustine and O\textsuperscript{6}-benzylguanine (BG) into poly (lactide-co-glycolides) nanoparticles (PLGA/CS NPs) was reported to enhance the efficiency of carmustine\textsuperscript{20}. By using electrojetting technique, microencapsulation of 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU, Carmustine) into poly(lactic-co-glycolic) acid (PLGA) was carried out. The microcapsules, thus obtained, had higher encapsulation efficiency, more drug loading capacity and narrower size distribution\textsuperscript{21}. The role of O(6)-methylguanine-DNA methyltransferase (MGMT) promoter methylation in glioblastoma patients treated with carmustine (BCNU) wafer implantation is unclear. Thirty patients were selected with newly diagnosed glioblastoma and seventeen with recurrent glioblastoma. They all were treated with BCNU (bis-chloroethylamine) wafers. Patients with newly diagnosed glioblastoma received first-line BCNU while 17 patients received concomitant and adjuvant temozolomide (TMZ) radiochemotherapy (first-line BCNU+TMZ). Out of 17 patients, 16 received radiotherapy with concurrent and adjuvant TMZ. The combination of TMZ radiochemotherapy with local delivery of BCNU did not provide benefit in survival compared to local BCNU alone\textsuperscript{22}. Carmustine wafers were studied in combination with 6-month metronomic temozolomide and radiation therapy in patients with newly diagnosed glioblastoma. As compared with Stupp regimen, this treatment was reported to produce promising results in terms of PFS without any notable increase in toxicities. However, the gain in median survival was not clear\textsuperscript{23}. The study of the growth pattern of tumor recurrence in a large group of patients (41 in number) was carried out. Recurrences were morphologically categorized as local, diffuse, distant or multilocular. Eighty percent of the tumors were reported to be local. It was
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concluded that BCNU implantation did not provide lasting local tumor control and the need to incorporate BCNU into multimodal therapeutic schemes was suggested. Development of biodegradable poly[(d,l)-lactide-co-glycolide] nanofibrous membranes was reported via electrospinning. It helped in release of BCNU. In vitro and in vivo release behaviours of pharmaceuticals released from the electrospun membranes were characterized by an elution method and HPLC assay. In rats, release of high concentrations of BCNU in the cerebral cavity was observed for more than 6 weeks. Hence, it proved to be effective in the delivery of drug for a longer time. Focused ultrasound (FUS) in the presence of microbubbles (MBs) was reported to open blood-brain barrier (BBB). It resulted in increase of chemotherapeutic drug delivery in brain parenchyma for glioblastoma treatment. Novel VEGF-targeting, drug-loaded MBs were reported that further increased drug release and reduced tumor progression in a rat model. Multimodal treatment including implanted carmustine chemotherapy and concomitant radiochemotherapy with temozolomide was investigated to yield better rates of survival than those described when carmustine/temozolomide were used alone. The use of carmustine in primary cerebral rhabdomyosarcomas (cRMS) was reported to help local control of the disease. The combination of 3-bromo-2-oxopropionate-1-propyl ester (3-BrOP) with carmustine effectively killed glioblastoma stem cells (GSCs) via depletion of ATP of cells and suppression of carmustine-induced DNA repair. The combination impaired the sphere-forming ability of GSCs in vitro and the ability to form tumor in vivo. It increased overall survival of mice having orthotopic inoculation of GSCs. Severe energy crisis was also noted in GSCs due to inhibition of glyceraldehydes-3-phosphate dehydrogenase. Investigation was carried out to report the use of a targeted nitric oxide (NO) donor to sensitize glioma cells to chemotherapy. The derivative of the protein chlorotoxin (CTX), CTX-NO, was developed. The cells were pretreated with CTX-NO followed by 48-h exposure to carmustine or temozolomide. It showed enhanced effectiveness of both the drugs. T98G and U-87MG human glioma cells exhibited pronounced sensitivity to drugs. The combinatorial study decreased levels of MGMT, changed p53 activity and reduced cell invasion. Co-administration of temozolomide, carmustine and doxorubicin along with vanilloid type 2 (TRPV2) against cannabidiol (CBD)-induced TRPV2 activation enhanced uptake of drug and in human glioma cells it potentiated cytotoxic activity.

Studies done in 2012

For pro-drug therapy, extracellular β-glucuronidase (β-GUS) in tumors has been reported to be a target enzyme. A single dose of a cytostatic drug like carmustine and doxorubicin in small C6 glioma tumors induced release of β-GUS. It resulted in increased efficiency of the pro-drug treatment. The efficiency and toxicity of a combination of procarbazine, carmustine and vincristine (PBV) was studied for 69 patients suffering with recurrent/progressive glioblastoma after surgery, concomitant radio/chemotherapy and adjuvant first-line temozolomide therapy. Of total 41 patients evaluable for response by MRI, one showed partial response, three showed minor response, ten exhibited stable disease for at least 6 weeks and twenty seven showed immediate progression. Fifteen weeks was noted as the median PFS and 21% for PFS-6 for fifty seven patients. After application of the first PBV cycle, twelve other patients were lost to follow-up. In 26% and 26% of cycles, grade III or IV leucopenia and grade III or IV thrombocytopenia were respectively observed. Interruption of treatment for 7% patients was observed due to haematological complications and moderate non-haematological complications were seen. For newly diagnosed and recurrent glioblastomas the effectiveness of Gliadel wafers was reported but the toxicity after the treatment was found to be higher. Treatment with BCNU and Gamma Knife radiosurgery (GKRS) was reported to be effective in local tumor control as when either BCNU or GKRS was used alone. The use of carmustine wafers was reported to be neither associated with more frequent complications nor
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decreased use of chemoradiotherapy. The survival and relapse rates in forty three immunocompetent patients of age less than 67 years were investigated. All the patients had newly diagnosed primary central nervous system lymphoma (PCNSL) and they were treated by two different high-dose methotrexate-based protocols along with high-dose carmustine/thiotepa (BCNU/TT) plus ASCT (+whole brain irradiation). High survival rates were recorded in patients with newly diagnosed PCNSL. Patients with newly diagnosed GBMs were reported to be subjected to dose-escalation study of I-125 seeds in a small group of 6 patients. Maximum number of BCNU wafers was surgically placed along with high doses of cGy (3000, 6000 and 9000). Followed by temozolomide chemotherapy, patients went through standard fractionated radiation to 5,940 cGy postoperatively. The trial was stopped as three of five patients developed radiation toxicity and they went through steroids+bevacizumab treatment. Two patients developed local disease progression. The use of seed-wafer therapy was not suggested for newly diagnosed GBM patients due to high (60%) incidence of early radiation toxicity. The tumors found in the central nervous system were treated successfully with semustine (MeCCNU) and carmustine (BCNU). Treatment of glioblastoma multiforme in infant using high doses of carmustine has been reported. Microbubble(MB)-enhanced focused ultrasound (FUS) was reported to cross blood-brain barrier effectively in the form of BCNU-MBs. A group of 110 patients of high-grade glioma treated via craniotomy and tumor resection was studied retrospectively. Carmustine wafers were placed in half of the patients and the remaining half received first-line systemic chemotherapy. A median survival of 13.414 months was shown by patients treated with carmustine wafers as compared to 11.047 for those who were not treated. The combination therapy of implantation of a BCNU-loaded wafer and intracarotid perfusion of BCNU-loaded nanoparticles was reported to be a successful strategy for glioma gene therapy. In high grade glioma, adding carmustine wafers before Stupp protocol was reported not to improve survival.

Studies done in 2011

In one study, twenty children were taken, of which 13 were diagnosed with astrocytoma and 7 with medulloblastoma. The children with astrocytoma were subjected to tumor resection surgery and the second group went through surgery and chemotherapy (Vincristine, Cisplatin and Carmustine) and radiotherapy (total dose of 54 Gy). Exposure to radiotherapy showed a significant effect on processing speed and on intellectual capacity. The efficacy of regional chemoinfusion in combination with radiation therapy in patients with breast cancer with metastases to the brain was reported by giving carmustine (100 mg) along with radiation therapy. A study was reported in which 43 patients of high-grade glioma underwent surgical removal and BCNU wafer implantation. Clinical, surgical and radiological data of 9 patients was retrospectively. These patients were treated with carmustine wafers after surgical repair of communication between the surgical cavity and the ventricular cavities. Crucial issues were recorded regarding integrity of wafers, size of ventricular wall defect and accuracy in repairing the defect. A combination therapy of small interfering RNA (siRNA) against Rex-1 (siRex-1) and BCNU was reported to target GBM cells. The result was growth suppression and diminished S phase. In vitro and in vivo apoptosis and induction of P38/JNK and Akt/P13K/GSK3β was seen. The treatment targeted both major population and cancer stem cell-like subpopulations. Older GBM patients were reported to benefit from carmustine wafers and the survival of older patients receiving carmustine wafers was more than those who did not receive. For recurrent brain tumors in children, a phase I trial of two cycles of HDC/SCR was performed to estimate the maximum tolerable doses for thiotepa which was 600 mg/m(2) and carmustine which was 300 mg/m(2) followed by thiotepa [600 mg/m(2)] and carboplatin [1,200 mg/m(2)]. Prolonged time to progression for a considerable number of patients was reported along with long-term survival for patients with recurrent medulloblastoma and rhabdoid tumor. Post-operative seizures were
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reported to be less in BCNU-treated patients\textsuperscript{52}. The combination of local chemotherapy with Gliadel wafers (7.7 mg) and radiotherapy and chemotherapy using temozolomide (TMZ) proved to be safe without any complication\textsuperscript{53}. Carmustine wafers have been reported to be effective in the treatment of high grade glioma too\textsuperscript{54}. Inhibition of human brain malignant glioblastoma cells using carmustine-loaded catanionic solid lipid nanoparticles with surface anti-epithelial growth factor receptor was reported\textsuperscript{55}. Space-occupying cyst development in the resection cavity of malignant gliomas following Gliadel implantation was found to be successful\textsuperscript{56}.

Studies done in 2010

A study was carried out to identify prognostic factors and test the effect of treatment on patients’ survival with high-grade glioma. Medical records of 36 patients were reviewed and 27 were included on survival analysis. Male:female ratio was 1:1 and mean age of diagnosis was 41.86 years. Anaplastic glioma was found to be 22.20%, glioblastoma multiforme 63.90% and mixed glioma was 13.90%. Seventeen patients had partial resection, fifteen had total tumor removal and in four patients only biopsy was carried out. Two third patients received radiotherapy and nine received chemotherapy with 3 BCNU and 6 temozolomide. Median follow-up time, overall survival time and median disease free survival time was 413.2 days, 604.04 days and 402.45 days, respectively. Histological findings of glioblastoma multiforme (GBM) and mixed glioma, received radiotherapy were the prognostic factors identified in univariated analysis. Radiotherapy improved overall survival in multivariate analysis. By increasing number of patients results could be improved\textsuperscript{57}.

CONCLUSION

There are a number of types of brain tumor. The most aggressive type of brain tumor is glioblastoma multiforme (GBM). The use of chemotherapeutic agents gets limited due to blood-brain barrier and toxicity limit. Gliadel wafers are helpful in crossing blood-brain barrier and increase local control and survival in newly diagnosed GBM patients. But, they have high complication rates too so, as yet, use of Gliadel wafers in GBM patients is not much suggested and more research needs to be carried out to find a safer alternative to these wafers. In patients with malignant gliomas, BCNU-impregnated biodegradable polymers have been found to increase survival time. After carmustine wafer insertion the reasons of post-operative haematoma are unclear and further studies are needed in this field. The role of O(6)-methylguanine-DNA methyltransferase (MGMT) promoter methylation in glioblastoma patients treated with carmustine wafers needs clarity. Integrity of wafers, size of ventricular wall defect and accuracy in repairing the defect require to be clarified both in what measure ventricular opening affects safety data and the best reliable way of repairing ventricular defects when BCNU wafers are implanted. The integration of chemotherapy with carmustine wafers and radiotherapy and chemotherapy with temozolomide requires more follow up study for promising results.

REFERENCES

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