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Case Report

Case Report on Survival of Patient with Glioblastoma Multiforme After Incomplete Resection and Role of Bevacizumab

Aiman Majid[1]*, Syed Bassim Zahid[2], Taimur Arain[3], Naila Zahid[4] and Falak Shahab[1]

[1]Medical oncologist, Liaquat national Hospital, Pakistan

[2]Agha Khan university Hospital, Pakistan

[3]M.B.B.S, Ziauddin University Hospital, Pakistan

[4]Head of Department oncology, Liaquat National Hospital, Pakistan

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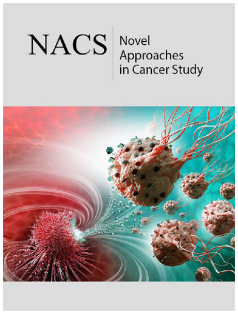

***Corresponding author:** Aiman Majid, Medical oncologist, Liaquat National Hospital, Pakistan

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Abstract

Aggressive brain tumor i.e. Glioblastoma multiforme has been known to be having poor prognosis with maximum therapeutic trial. A number of studies have already been published showing improvement in survival after maximal safe resection followed by adjuvant CCRT in terms of improving survival in years but the overall prognosis of glioblastoma multiforme is dismal. In this case, a lady un-fortunately had not gone through complete resection of the tumor because of the tumor location then she received adjuvant treatment with concurrent chemo-radiation with temozolomide followed by continuation of temozolomide alone for a total of 17 cycles after she had disease progression then she was switched to bevacizumab. So far, she has received 2 weekly total of more than 35 cycles with stable disease status without toxicity. Up till now, she has passed more than 5 years without any deterioration in her performance score. Despite the fact that GBM has a dismal prognosis and maximum survival is 3 years. In the future, more research will be required to determine the role of other VEGF inhibitors in recurrent settings as well as upfront settings. This case gives a stimulus to make some more effort to improve survival for future cases of GBM.

Introduction

Glioblastoma multiforme (GBM) is a competitive malignant number one mind tumor. It is characterized by rapid growth, infiltrative behavior, and high resistance to treatment. Despite advancement in treatment modalities, the prognosis of GBM remains poor, with a median survival of approximately 12 to 15 months following diagnosis and management with combined modality treatment. Surgical resection is typically the initial treatment approach, aiming to achieve maximal safe tumor removal. However, complete resection is often challenging due to the infiltrative nature of GBM [1].

Because of the infiltrative nature of the tumor as well as complete resection is not feasible in most cases, adjuvant therapies are employed to target residual tumor cells and delay disease progression. Adjuvant treatment includes radiation and systemic therapies. The systemic therapy approach now depends on molecular characteristics of the disease which include O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation and isocitrate dehydrogenase (IDH) type 1 or type 2 mutations. Methylation of the MGMT promoter, which is relevant to treatment selection as well as prognosis while IDH only predicts survival. Another factor that will predict survival and help in deciding adjuvant treatment options includes age of the patient and functional status [2].

Temozolomide is considered as one of the most efficacious agents for glioblastoma with concurrent and adjuvant treatment for glioblastoma multiforme in both MGMT-methylated tumor and un-methylated tumors [2].

Another therapeutic agent under consideration for adjuvant treatment is of bevacizumab, a monoclonal antibody targeting vascular endothelial growth factor (VEGF). Bevacizumab, with its anti-angiogenic properties targeting vascular endothelial growth factor (VEGF), acts by inhibiting growth of tumor and angiogenesis, possibly contributing to disease stability in GBM patients [2]. The efficacy of bevacizumab in the treatment of GBM has been a topic of discussion. While initial clinical trials demonstrated encouraging results, but some later studies have reported mixed outcomes and raised concerns regarding the optimal patient's selection, potential toxicities and long-term survival benefits.

In this case report, we present the unique case of a patient diagnosed with GBM who underwent incomplete resection due to the infiltrative nature of the tumor. The patient received bevacizumab injections as part of their treatment regimen, resulting in stable disease and an exceptional 5-year survival. This case highlights the potential role of bevacizumab in achieving disease stability and its impact on long-term survival in GBM patients and need further researches to look into the role of other VEGF inhibitors. The purpose of this report is to provide a detailed description of the patient's clinical course, treatment approach, imaging findings, and outcomes. Additionally, we aim to contribute to the existing literature on the use of bevacizumab in GBM treatment, discussing the potential benefits, limitations, and future research directions in this field.

Case Presentation

A case of 56 years old female known case of hypertension and depression, had a history of vertigo, headache, left-eye decreased vision and left-sided upper and lower limb weakness for 2 months, she was advised for an MRI brain which showed an ill-defined abnormal signal intensity lesion identified in the right occipital region. It approximately measures 3.7 x 2.2cm in maximum dimensions. Another fronto-parietal lesion appears intermediate on T2W images, this is associated with a well-defined cystic component which measures 7 x 4.3 cm in maximum dimensions. With perilesional edema and mass effect over ipsilateral lateral ventricle, brain stem, and adjacent brain parenchyma with the contralateral midline of 1.1 cm.

After pre-op anesthesia, the patient underwent neuro-navigation-guided right occipital craniotomy + fluorescein-guided tumor excision on 23rd May 2018.

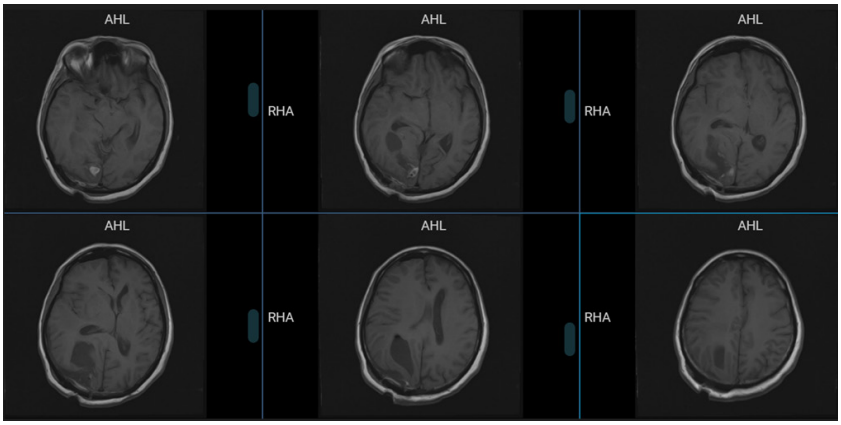
Intraoperative findings were: cystic portion aspirated (greenish yellow color), occipital lobe sunken as fluid aspirated, solid component soft to firm yellowish mild to moderately vascular was excised.

Histopathology showed: an anaplastic hypercellular glial tumor composed of a poorly differentiated, pleomorphism astrocytic tumor with marked nuclear atypia and brisk mitotic activity. Prominent microvascular proliferation and necrosis is present. Few areas showed hyalinized blood vessels with extensive calcification.

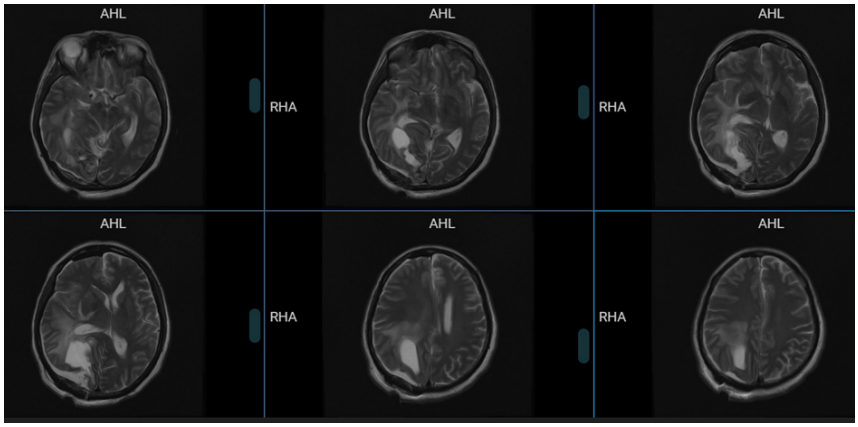
Immunohistochemical stains: olig 2 positive, IDH 1 wild type, cytokeratin negative, ki-67 proliferative index of 10-15%.

Diagnosis: glioblastoma multiforme, WHO grade IV, wild type.

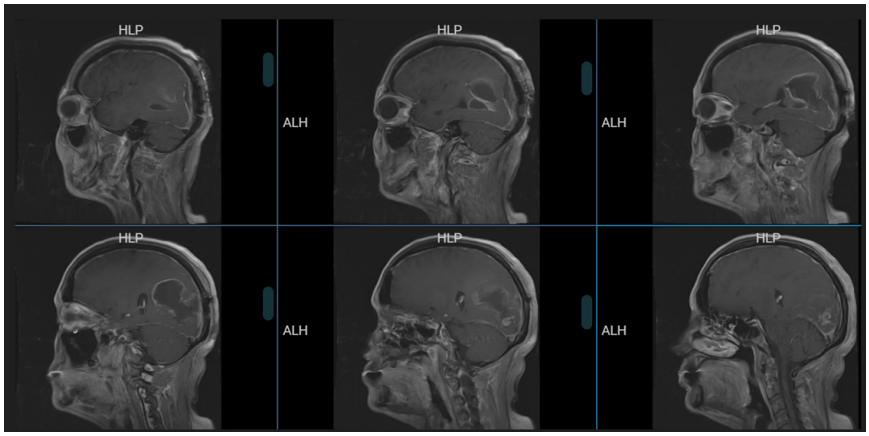
Post- op MRI showed (Figure 1)



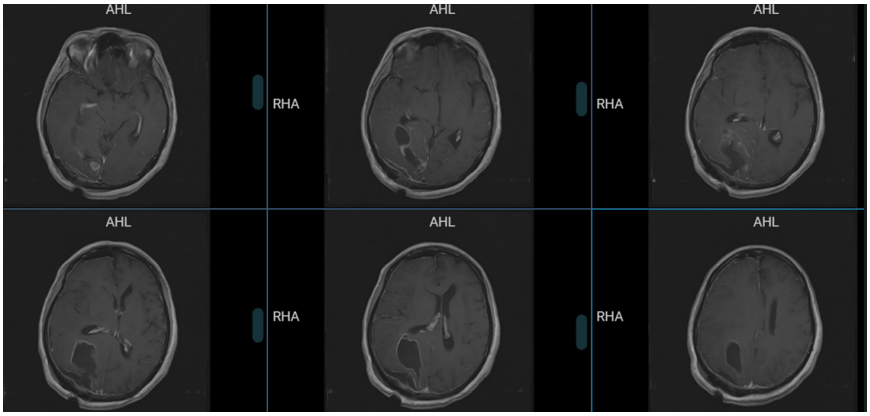
Axial T1-weighted images showing post surgical changes in the right parieto-occipital region. T1 hypointense lesion seen in right parietal, occipital and temporal lobes, reaching up to the trigone and causing mass effect over it. A small nodular high signal intensity lesion is noted in right occipital lobe.



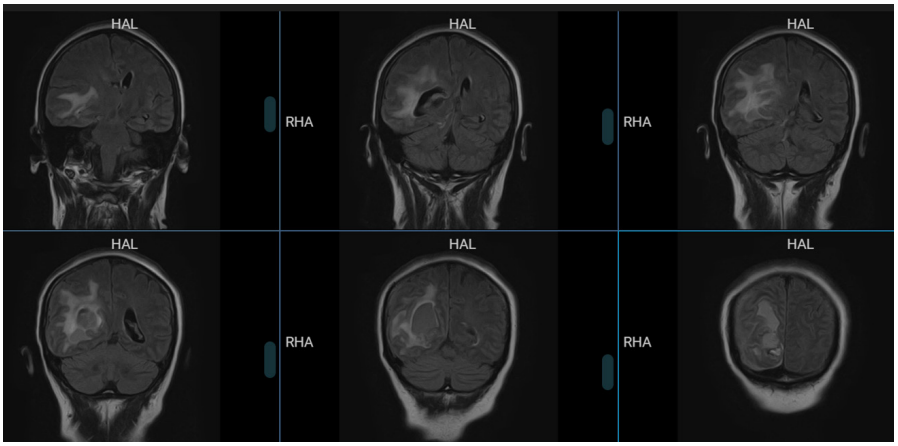
Axial T2-weighted images showing post surgical changes in the right parieto-occipital region. T2 hyperintense lesion seen in right parietal, occipital and temporal lobes, reaching up to the trigone and causing mass effect over it. A small nodular iso to low signal intensity lesion is noted in right occipital lobe.



Sagittal T1 postcontrast sections showing post surgical changes in the right parieto-occipital region. Cystic lesion seen in right parietal, occipital and temporal lobes showing smooth rim enhancement, reaching up to the trigone and causing mass effect over it. Some nodular enhancement is also noted in right occipital lobe.



Axial T1 postcontrast sections showing post surgical changes in the right parieto-occipital region. Cystic lesion seen in right parietal, occipital and temporal lobes showing smooth rim enhancement, reaching up to the trigone and causing mass effect over it. Some nodular



FLAIR coronal sections showing lobulated isointense lesion in the right occipital lobe reaching up to the trigone of right lateral ventricle with mass effect and midline shift. Significant perilesional FLAIR hyperintensity also noted reaching upto right temporal lobe

Figure 1

She had left homonymous hemianopia post-operatively, her asterognosis and agraphisthesia was improved.

Patient then received concurrent chemo-radiation with temozolomide till October 2018 followed by adjuvant temozolomide x 17 cycles till October 2020. Then she had radiological disease progression with interval increase in size, edema and enhancement of lesion with pressure effect. For which she underwent SRS first (35Gy in 5 fraction) bevacizumab 10mg/kg x 2 weekly x 4 cycles till December 2020, followed by lost to follow up. She again then presented to us on November 2021 which showed disease progression, with some balance issues. She then restarted on bevacizumab again. So far, she has received 35 cycles and her last scan showed stable disease. Currently she has some balance issues otherwise maintaining a good quality of life.

Discussion

Complete surgical resection is the primary treatment approach for glioblastoma multiforme; however, achieving complete resection can be challenging due to the infiltrative nature of GBM cells. In the case report presented, we explore the survival of a patient who underwent incomplete resection of GBM and the role of bevacizumab in their treatment. Surgery plays a crucial role in GBM treatment, aiming for maximal resection. Surgery followed by radiation therapy is the standard of care for GBM. However, even

with maximal safe resection, the majority of patients experience tumor recurrence. In our case, the patient underwent an incomplete resection, which is associated with a higher risk of recurrence. The survival benefit of surgery and radiation therapy alone varies, with reported median overall survival ranging from 9 to 15 months in relapse cases An incomplete resection leads to the presence of residual tumor cells, affecting patient prognosis. Factors such as tumor location and involvement of eloquent areas may limit the extent of resection. Radiation therapy is often employed as an adjuvant treatment following surgery to target residual tumor cells and microscopic disease. Different radiation techniques, including whole-brain radiation and stereotactic radiosurgery, have shown variable efficacy in improving overall survival rates. The standard chemotherapy regimen for GBM involves temozolomide, which in combination with radiation therapy, has shown modest benefits. However, its efficacy is limited, particularly in cases of incomplete resection.

In our case, we are focusing on the treatment options for GBM with its associated outcome. Despite multimodal treatment options including surgical resection, adjuvant postoperative RT with concurrent chemotherapy, and adjuvant chemotherapy prognosis is mostly grave. Some patients may achieve remission but ultimately the disease is relapses in most cases. The role of temozolomide in GBM after resection is well explained. Temozolomide, an oral alkylating agent, is commonly used as a chemotherapeutic agent in GBM. In the adjuvant setting, temozolomide has been shown to improve overall survival. In relapse cases, the use of temozolomide as salvage therapy has demonstrated a survival benefit, with reported median overall survival ranging from 6 to 12 months [3,4]. Targeted Therapies: Bevacizumab, an anti-angiogenic agent targeting vascular endothelial growth factor (VEGF), has shown promise in recurrent GBM. Several clinical trials have evaluated the efficacy of bevacizumab as monotherapy or in combination with other agents. In relapse cases, bevacizumab has demonstrated modest improvement in progression-free survival but has shown limited impact on overall survival, with reported median overall survival ranging from 6 to 9 months Either concurrent with radiation or adjuvant after resection. In a study, Navid Redjal et al. [3] concluded that temozolomide, in combination with radiotherapy as per the Stupp protocol, is a crucial treatment for younger glioblastoma patients. This approach might also hold promise for those over 70. However, the role of BCNU wafers post-resection within the Stupp protocol remains uncertain [3]. In further studies we have seen that the addition of bevacizumab to radiotherapy-temozolomide showed improved progression-free survival and preservation of baseline quality of life and performance status, it did not lead to enhanced overall survival in patients with glioblastoma. The study revealed higher rates of adverse events associated with bevacizumab compared to placebo, indicating that the treatment's benefits were accompanied by increased risks [4]. So, the role of anti-angiogenic treatment including bevacizumab in upfront adjuvant setting is not proven. Malaka Ameratunga et al. [5] also concluded that anti-angiogenic therapy does not significantly enhance overall survival in newly diagnosed glioblastoma patients. Thus, evidence is insufficient to support its use for this purpose. Although bevacizumab extends progression-free survival, its impact on patients' quality of life and net clinical benefit remains uncertain [5].

Mark R Gilbert et al. [6] investigated that the first-line use of bevacizumab did not lead to improved overall survival in patients with newly diagnosed glioblastoma. Although progression-free survival was prolonged in the bevacizumab group likely due to decreased angiogenesis ultimately decreasing surrounding peri-lesional edema, it did not meet the pre-specified improvement target. The study revealed that while bevacizumab had some benefits, including longer progression-free survival, it was associated with increased rates of adverse events and a decline in quality of life and neurocognitive function over time [6]. In another study, the role of addition of lomustine to bevacizumab led to a somewhat prolonged progression-free survival as compared to lomustine alone, but it did not confer a significant survival advantage over lomustine monotherapy for patients with progressive glioblastoma. Adverse events were more prevalent in the combination group, and the addition of bevacizumab did not have a substantial impact on overall survival [7].

The role of bevacizumab in relapse second-line setting of GBM is well established, regarding the dose of bevacizumab, Victor A Levin et al. [8] concluded that dosing bevacizumab (BEV) at half the standard dose for progressive/recurrent glioblastoma (GBM) was at least equivalent to, or possibly better than standard dosing. Their retrospective analysis of patients treated with BEV revealed that patients treated below the median administered dose of BEV had better outcomes compared to those treated above the median dose. Additionally, female patients demonstrated longer overall survival with BEV than males, while patients over 65 years and those starting BEV after chemo-radiation had worse outcomes [8].

Abdulrazag Ajlan et al. [9] concluded that optimizing the dosing of bevacizumab (BEV) in glioblastoma could lead to better outcomes. Through their study of 80 patients, they found that using lower doses of BEV (<3mg/kg/week) resulted in significantly fewer serious adverse events compared to higher doses (≥3mg/kg/week). Additionally, patients receiving lower doses had better survival rates, although not statistically significant. This suggests the potential for reducing complications while maintaining positive clinical impact by using lower BEV dosages in glioblastoma treatment. Further research to refine BEV dosage is warranted [9].

Jeffrey J Raizer et al. [10] concluded that an every-3-week schedule of bevacizumab demonstrated antitumor activity and tolerable toxicity in patients with recurrent high-grade gliomas. The study included patients with glioblastoma multiforme and anaplastic glioma, with a median number of previous chemotherapies being [2]. The observed toxicities were primarily grade 1 and 2. The 6-month progression-free survival rate for GBM patients was 25%, with a median time to tumor progression of 10.8 weeks and overall survival of 25.6 weeks. Tumor VEGFA/VEGFR2 ratio increase was correlated with decreased survival. These

findings suggest the potential efficacy of the bevacizumab schedule in this patient population [10].

Eric T Wong et al. [11] concluded that their meta-analysis of 15 studies on bevacizumab for recurrent glioblastoma multiforme revealed consistent efficacy benchmarks. Median overall survival was 9.3 months, with 6-month progression-free and overall survival rates at 45% and 76%, respectively. The median time to tumor progression was 6.1 months. Response analysis indicated 6% complete response, 49% partial response, and 29% stable disease. No significant difference in efficacy was observed between different bevacizumab doses. The study's findings aligned with those of recent randomized phase II studies. However, the lack of a dose-response effect requires further investigation in prospective clinical trials [11].

In our patient's case, molecular testing allowed for the identification of potential therapeutic targets and informed the decision to administer bevacizumab. The integration of molecular testing into clinical practice has the potential to improve patient outcomes by identifying specific genetic alterations and enabling targeted therapeutic interventions. It is worth noting that this case report represents a single case, and caution must be exercised when interpreting the results. Larger studies and clinical trials are needed to validate these findings and establish the efficacy of bevacizumab in GBM treatment after incomplete resection. Additionally, the limitations of bevacizumab, such as the development of resistance and potential adverse effects, should be taken into consideration when determining its appropriate use.

Sirtuin 1 (SIRT1) has a complex role in glioblastoma, where high expression is often linked to tumor growth, chemoresistance, and poorer survival, but in some cases, elevated levels associate with better outcomes. This dual effect depends on factors like the tumor environment and genetics. Monitoring plasma SIRT1 could provide a useful biomarker for prognosis and personalized treatment in GBM [12].

Conclusion

In conclusion, we present a compelling case of a patient with glioblastoma multiforme (GBM) who achieved a remarkable survival outcome following an incomplete resection and treatment with bevacizumab. The place of interest in this case is the possible benefits of bevacizumab in attaining disease stability and extending survival in GBM patients. Despite the aggressive behavior of this tumor and in general, associated with poor prognosis, the use of bevacizumab in a second-line setting in this particular case resulted in a notable 5-year survival. Although the role of bevacizumab in GBM treatment is already proven, this case provides valuable insight into the potential benefits it may offer, particularly in patients with incomplete resection and a clinical.

Further studies and clinical trials will be needed to better understand the optimal dogmata for incorporating bevacizumab into GBM treatment protocols, I.e. Finding predictive biomarkers, exploring combination therapies and evaluating long-term outcomes. Furthermore, exploring the underlying mechanisms of resistance and pointing to potential challenges associated with bevacizumab therapy, will be important for improving patient outcomes. Additionally, targeted molecular agents, such as EGFR inhibitors or IDH1 inhibitors, are being explored in specific molecular subtypes of GBM. However, their efficacy is still under investigation and survival benefits in relapse cases are not yet well-established.

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