Case Report

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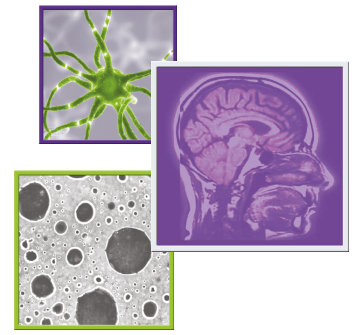

Very long-term survival of an older glioblastoma patient after treatment with cilengitide: a case report

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Glioblastoma (GBM) is the most common malignant brain tumor. Less than 1% of patients survive longer than 10 years. A 77-year-old woman was diagnosed with MGMT-methylated GBM in 2009. The patient received cilengitide as part of the CENTRIC clinical trial in conjunction with standard radiation and chemotherapy. Though the study was halted in 2013, our patient received cilengitide until 2016 with no radiographic evidence of recurrence thus far. This is the oldest reported GBM patient with greater than 10-year survival. Her exceptional response may have been influenced by MGMT promoter methylation status and PTEN expression.

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Glioblastoma (GBM) is the most common malignant CNS tumor accounting for 49.1% of all primary CNS tumors with prevalence of 3.23 per 100,000 in the USA [1]. The current standard treatment for GBM consists of surgical resection followed by radiation therapy with concurrent temozolomide chemotherapy, followed by adjuvant cycles of temozolomide chemotherapy, with the optional addition of tumor-treating fields [2,3]. The overall survival (OS) rate is 6.8% at 5 years and 0.71% at 10 years [1]. As such, long-term survivors (LTS) of GBM have garnered great interest. The definition of 'long-term survival' varies by study but is often used to refer to GBM patients who have survived more than 3 years after diagnosis. Over the past few decades, different therapeutic approaches such as angiogenesis inhibitors, immunotherapies, targeted therapies, and vaccines have been evaluated in clinical trials for patients with newly diagnosed or recurrent GBM with a modest improvement in OS and PFS. Promising results emerged for the addition of tumor treating fields to standard therapy. Studies showed an increase in median OS by approximately 5 months in newly diagnosed GBM [4].

Prior studies have assessed biomarkers that are associated with improved prognosis, yet it has been challenging to study the characteristics of LTS of GBM due to the small pool of patients. A previous study concluded that the factors associated with LTS are younger age at diagnosis, Ki-67 less than 10%, presence of mutations in *IDH1/2* and *ATRX*, wild-type *TERT* promoter and methylated *MGMT* promoter status. Young age and *MGMT* promoter methylation status are the only statistically significant predictors of very LTS [5].

First identified in the 1970s, integrins are a class of transmembrane receptors that are composed of an alpha and a beta subunit. Different combinations of alpha and beta subunits produce 24 different integrin receptors and are classified based on cell attachment site sequence and cell of expression. Integrins are important in tumorigenesis as they play an important role in tumor migration, adhesion and signaling. Integrins become active once a ligand is attached to either the intracellular or the extracellular domain of the receptor [6].

Integrins have been studied in different cancers such as brain tumors, melanoma, prostate and colorectal cancer. Integrin-targeted therapies have also been studied and approved for the treatment of cardiovascular disease, inflammatory conditions and dry eye disease. Specific integrins, namely αvβ3, αvβ5 and αvβ1, are important in angiogenesis in glioma [7]. The cyclic RDG containing pentapeptide with molecular formula $C_{27}H_{40}N_8O_7$, cilengitide, is a selective αvβ3 and αvβ5 integrin inhibitor. Cilengitide has been evaluated in several GBM studies [8].

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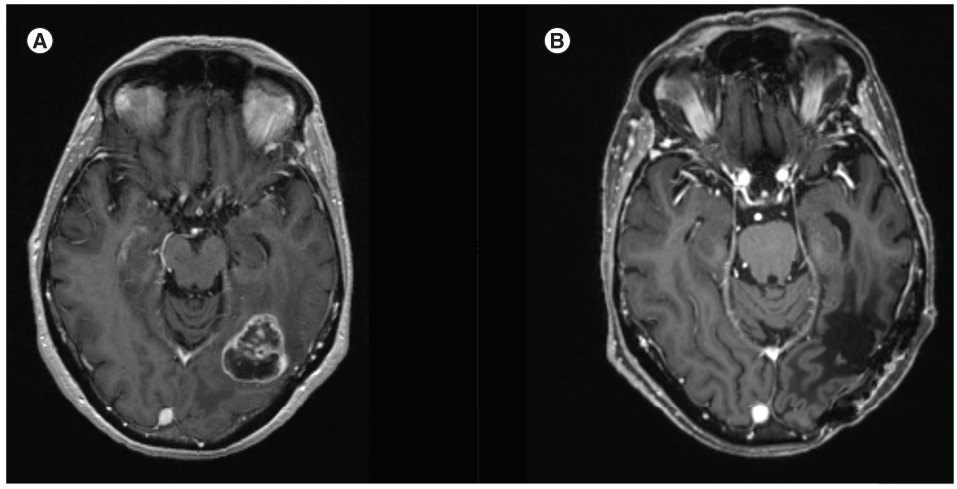

Figure 1. Brain MRI, postgadolinium enhanced T1-weighted axial imaging. (A) Baseline MRI at time of diagnosis in 2009 showing a 3.8 × 3.2 × 3.2 cm peripherally enhancing left temporoparietal mass. **(B)** Surveillance MRI in January 2022 showing surgical resection cavity and gliosis in the left posterior temporal-occipital region with no mass effect or abnormal enhancement.

Following a preclinical study that demonstrated cilengitide's ability to halt GBM growth in a xenograft mouse model [9], a Phase I/II clinical trial of cilengitide in 52 patients with newly diagnosed GBM demonstrated median OS of 16.1 months, which compared favorably to historical control [10]. A Phase II randomized trial of cilengitide plus standard chemoradiation in 112 patients with newly diagnosed GBM demonstrated good tolerability, with a median OS of 30 months in patients with MGMT-methylated tumors and 17.4 months in patients with MGMT-unmethylated tumors [11]. Results of the study found that cilengitide is well tolerated with the potential for improved outcomes in GBM patients [11]. These positive findings led to the development of two randomized clinical trials of cilengitide for patients with newly diagnosed GBM: the Phase III CENTRIC trial for patients with MGMT-methylated tumors, and the Phase II CORE trial for patients with MGMT-unmethylated tumors. In this case report, we present an older woman with methylated MGMT GBM who received cilengitide as part of the CENTRIC trial in conjunction with standard radiation and chemotherapy and has remained without recurrent disease thus far for more than 12 years.

Case presentation

In 2009, a 77-year-old woman presented for evaluation of progressive visual loss. Brain MRI was obtained which showed a left temporo-parietal tumor (Figure 1A). The patient had gross total resection of the tumor. Histopathology (Figure 2A–D) was remarkable for pseudopalisading necrosis, vascular proliferation, tumor giant cells, hypercellularity and atypical mitoses consistent with WHO grade IV GBM. *MGMT* methylation status was performed and confirmed at a licensed laboratory according to trial protocol using methylation specific PCR. Tumor cells were diffusely and strongly positive for *PTEN* and *MAPK*. Genetic testing (Tempus xT) performed in 2021 on the original biopsy sample demonstrated *TERT* promoter mutation (C124T) with variant allele frequency (VAF) of 29.0%, and a loss of function *TP53* mutation (G725A) with 52.6% VAF. No mutations were detected in *IDH1* or *IDH2*.

She enrolled in the multicenter, open-label Phase III clinical trial (CENTRIC) studying cilengitide in conjunction with standard radiation and temozolomide chemotherapy for newly diagnosed patients with *MGMT*-methylated GBM. She received the first dose of twice weekly 2000 mg iv. cilengitide infusions that are formulated in 0.9% sodium chloride solution in September 2009 and began adjuvant chemoradiation therapy the following week per protocol. The patient completed radiation and a 6-week course of temozolomide in November 2009. She completed a total of eight cycles of adjuvant temozolomide by July 2010. Brain MRI scans every 3 months showed stable findings with no evidence of recurrence. Her visual deficits improved, and she tolerated treatment well, with minimal adverse effects.

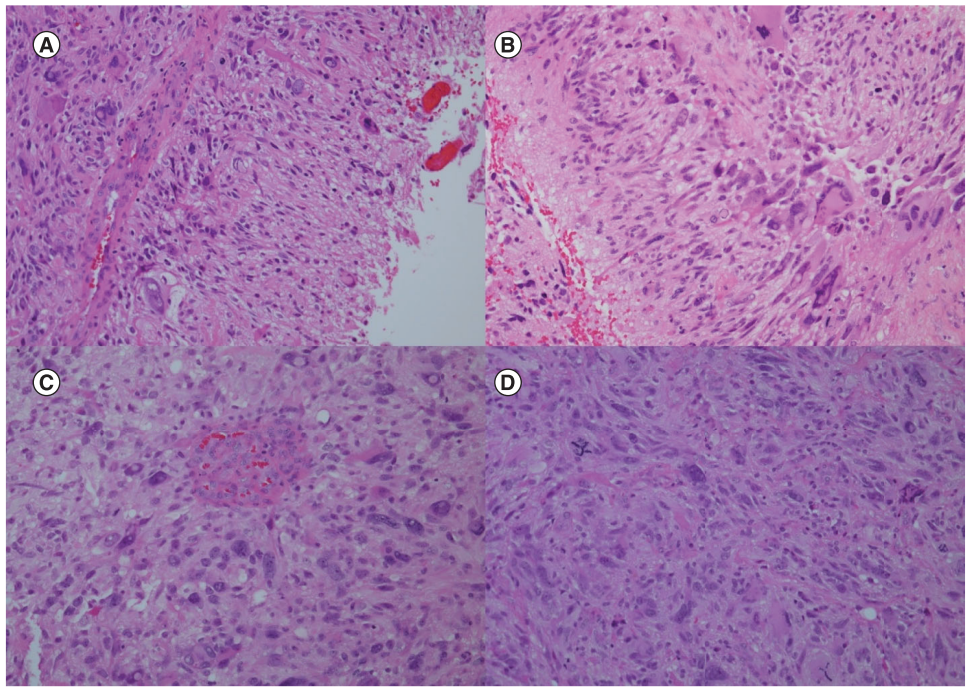

Figure 2. Histology of resected tumor at the time of diagnosis. (A) Pseudopalisading necrosis (right), vascular proliferation and tumor giant cells. **(B)** Pseudopalisading necrosis (left), tumor giant cells and mitosis. **(C)** Vascular proliferation, pleomorphic tumor cells and mitosis. **(D)** Hypercellularity with pleomorphic tumor cells, mitoses including atypical mitosis.

In early 2013, CENTRIC investigators reported that the study failed to improve overall- or PFS. The patient remained on cilengitide through compassionate use program following the closure of the CENTRIC trial. Over the years, she developed several pulmonary and urinary infections, recurrent falls and memory issues; none of these issues appeared to be related to cilengitide use. Cilengitide was briefly interrupted for leukopenia and neutropenia. She was incidentally found to have a chest wall angiosarcoma lesion which was excised and did not require further treatment. Cilengitide was interrupted for one and a half months during that time in 2016. The patient last received cilengitide in September 2016 due to drug discontinuation. In total, the patient received 377 sessions of cilengitide infusions. The patient has been having serial brain MRIs every 2–3 months since 2009 with no radiographic evidence of recurrence (Figure 1B). She maintains an ECOG of 1.

Discussion

The median OS in patients with GBM with methylated *MGMT* promoter status is 31.6 months compared with 16.9 months in those with unmethylated status with the current standard of care therapy [12]. In older patients over the age of 60, median OS is significantly lower at 13.5 months despite harboring a methylated *MGMT* promoter [13]. In a recent systematic review, the rate of survival for more than 10 years was found to be less than 1%, and none of the subjects out of 162 that were included in the study were older than 70 at the time of diagnosis [14].

Cilengitide is an integrin inhibitor targeting αvβ3 and αvβ5. Integrins play an important part in supporting cancer cells in migration and angiogenesis through the *TGF-β* pathway. Multiple preclinical and Phase I and II trials were conducted and demonstrated the safety and potential efficacy of cilengitide [15]. Therefore, several randomized controlled clinical trials were conducted to study cilengitide in GBM.

To our knowledge, this case report highlights the oldest reported patient with GBM with more than 12 years of survival with no evidence of recurrence. In addition to receiving standard therapy with maximal surgical resection and chemoradiation therapy, the patient was part of the multicenter Phase III clinical trial (CENTRIC) evaluating the impact of adding cilengitide on OS and PFS

The CENTRIC trial included patients with *MGMT*-methylated GBM, while a sister study – the CORE trial – enrolled patients with *MGMT*-unmethylated GBM. Patients in either study were randomized to receive

twice weekly infusions of cilengitide in addition to standard therapy of chemotherapy and radiation or to receive standard therapy alone. Both studies failed to detect improved PFS or OS in the treatment groups [16,17].

In the CENTRIC trial, the median age of enrollment was 58 years with an interquartile range of 50–65 years. Gross total resection of the tumor was performed in 49% of the patients. Cilengitide was started 1 week prior to the initiation of radiotherapy. Patients received cilengitide for a median of 55.6 weeks. Median OS was 26.3 months in both the study and control groups. Median PFS was 13.5 and 10.7 months in the study and control groups, respectively [16].

Comparatively, our patient was 77 years old at the time of diagnosis and underwent gross total resection of the tumor and received concurrent temozolomide chemotherapy and radiation therapy followed by 8 cycles of temozolomide. As per protocol, she received twice weekly infusions of cilengitide starting 1 week before the initiation of radiotherapy, from September 2009 to September 2016 with only a few weeks of interruption until the medication was discontinued by the manufacturer in 2016. Surveillance brain MRI scans since 2009 are without evidence of recurrence.

A follow-up study investigating integrin expression in the tumors of the patients in the CENTRIC and CORE trials found that integrin levels did not correlate with prognosis in patients with methylated *MGMT* promoter [18]. Other integrin inhibitors have been investigated but failed to improve outcomes, such as etaracizumab, an αVβ3 antibody inhibitor and volociximab, a β1 inhibitor [6]. Abituzumab, an αV inhibitor, was found to potentially have improved outcomes in select patients with high expression levels of the target molecule [6]. Cilengitide was also studied in recurrent or refractory high-grade glioma in children in a Phase I study that showed possible benefit, but a follow-up Phase II study failed to show improved survival [19,20].

Molecular profiling of this patient's tumor demonstrated a *TERT* promoter mutation. Mutations in *TERT* promoter are associated with various types of tumors, including GBM [21]. It has been investigated as a potential oncogenic driver owing to its role in maintaining chromosomal integrity in cancer cells. It is unclear yet what the prognostic implications of *TERT* mutations are. Some studies have found a worse prognosis for patients with GBM harboring *TERT* mutation with *IDH*-wildtype and methylated *MGMT* status [22].

PTEN expression was strongly positive in this patient's tumor. *PTEN* is a tumor suppressor gene and an essential regulator of *PI3K/Akt* pathway that controls cell growth and angiogenesis [23]. Therefore, the expression of *PTEN* has been associated with a more favorable prognosis [23].

MGMT protein is a DNA repair enzyme that repairs the damage caused by alkylating chemotherapies such as temozolomide. Tumor cells with methylated *MGMT* do not express the protein or express it at low levels, therefore making the tumor more susceptible to alkylating chemotherapy [24]. Though studies have consistently shown that patients with GBM with methylated *MGMT* promoter have improved outcomes, the prognosis in elderly patients remains poor. Our patient's exceptional response may have been influenced by the *MGMT* promoter methylation status and *PTEN* expression.

In addition to cilengitide, this patient received standard treatment with radiation therapy and temozolomide; thus, the relative contribution of cilengitide to this patient's clinical outcome is unclear. However, to our knowledge, this is the oldest reported GBM patient with greater than 10 year survival, and thus it is reasonable to suspect that the most unique aspect of this patient's treatment course (i.e., cilengitide) contributed substantially to this unique outcome.

Conclusion

Although cilengitide has failed to improve outcomes for patients with GBM, our case of a LTS proposes that integrin inhibition may still have clinical benefit for specific cases.

Summary points

- Long-term survival of more than 10 years is rare for patients with glioblastoma, especially in older individuals such as our patient.
- We have limited understanding of the extraordinary response of some patients to treatment in part due to the limited cases published of such patients.
- Our case highlights the importance of studying the patients and tumor characteristic of patients with exceptional responses to nonstandard therapies.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Informed consent disclosure

The patient provided their written informed consent to participate in this study. Written informed consent was obtained from the individual for the publication of any potentially identifiable images or data included in this article.

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