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Bevacizumab and Optune Combination in Treating Newly Diagnosed GBM: Case Study

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Abstract

Following Glioblastoma Multiforme (GBM) diagnosis, patients typically undergo surgical resection, followed by radiation with concurrent Temozolomide (TMZ) per the Stupp protocol as the standard-of-care. A 58-year old female patient at our institution, originally diagnosed with ER+, PR+, HER2+ Stage IB breast cancer, was later found to have a GBM tumor crossing the corpus callosum 6-months after completing radiotherapy for her breast cancer diagnosis. The patient was unable to tolerate TMZ due to persistent pancytopenia. Her White Blood Cell (WBC) count nadir was 400/mm^3 and her platelet count nadir was 11,000/L. The patient was started on Bevacizumab (brand name: Avastin) in combination with an Optune device following the completion of brain radiation treatment and upon retainment of normal blood cell counts. Her blood counts continued to remain normal; WBC counts ranging from 2,900 to 4,600/mm^3 and platelet counts ranging from 121,000 to 213,000/L while undergoing Avastin chemotherapy paired with the Optune device. The patient's imaging remains stable with a measurable mass of 5.7 cm × 3.2 cm × 5.5 cm compared to the 6.5 cm × 4.3 cm × 6.5 cm size of the mass at diagnosis. We propose this combination of therapy may useful upfront for patients diagnosed with large GBM tumors, or GBM tumors, that cannot be resected who cannot tolerate TMZ due to allergy or adverse reactions.

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Introduction

The patient is a 58-year old female, originally diagnosed with Stage IB (cT2, cN0, cM0) invasive ductal carcinoma of the right breast in 08/2016. Pathology revealed ER+, PR+, HER2+ hormone receptor status. In August of 2018, the patient completed neoadjuvant chemotherapy, Taxotere + Carboplatin + Herceptin + Perjeta (TCHP). She then underwent a partial right mastectomy in January of 2019 with 1 cm residual tumor and node negative disease. Following surgery, she started adjuvant Herceptin and Pertuzumab, and also received 52.56 Gy of radiation in 20 fractions to the right whole breast with a lumpectomy cavity boost, which was completed in 03/2019. Herceptin and Pertuzumab were stopped early due to GBM diagnosis in 09/2019. The patient started having word finding difficulty beginning early in 2019. Her first seizure was noted at the beginning of September; she went to the emergency room and was found to have a heterogeneous irregularly enhancing mass within the left frontal lobe, crossing the corpus callosum into the right frontal lobe with imaging characteristics most consistent with a high-grade glioma. The patient had a stereotactic biopsy which revealed a WHO grade IV glioblastoma IDH-1 R132H wild-type, and not methylated for MGMT. Her treatment plan was to follow the Stupp protocol. However, while being treated with radiation and concurrent Temozolomide (TMZ), the patient became pancytopenic requiring transfusion support as well as Filgrastim. The patient finished radiation therapy but stopped TMZ. For consolidation, the patient was initiated on Avastin. In April, the patient experienced proteinuria and was then changed to a 21-day cycle with treatment on day 1.

Materials and Methods

The patient is being treated at the University of Cincinnati Barrett Cancer Center for her GBM diagnosis as of 09/2019. She began the standard-of-care, which prescribed 60 Gy of radiotherapy

in 30 fractions concomitant with Temozolomide followed by twelve adjuvant cycles of Temozolomide [1]. TMZ was to be prescribed a dosage of 75 mg per square meter of body-surface area as per the Stupp protocol [1]. Chemotherapy treatment began day 1 of treatment but was stopped on day 23 of treatment due to pancytopenia. Therefore, instead of adjuvant TMZ, she was started on Avastin and the Optune device. The patient was able to complete IMRT photon therapy. Avastin was initially prescribed at a dose of 7.5 mg/kg then increased to 10 mg/kg after two doses, given on a 28-day schedule on day 1 and 15. This schedule was modified to a 21-day cycle with Avastin infusion on day 1 due to proteinuria. The Optune device utilizes Treating Fields (TTF) *via* 100 kHz to 300 kHz frequency electric fields with the goal to inhibit cancer cell mitosis [2]. The patient underwent various imaging used to monitor tumor progression. MRIs were conducted every 2 to 3 months.

Theory/Rationale

Physicians believed the Optune device would benefit the patient due to its known efficacy in increasing overall survival for patients diagnosed with GBM. Previous clinical trials suggest additional months of survival with Optune device alone, compared to those without [2]. In addition, there was benefit to increased progression-free survival for patients wearing Optune device than those who did not [2]. The Optune device also has correlated to patient compliance. Seeing as the patient had demonstrated compliance with previous continuous radiotherapy treatments, her care team thought she would be a good candidate for the device. In addition, previous studies showed that the Optune device had no negative impact on health-related quality of life [2]. Calculation of how the tumor progressed during the patient's treatment was monitored by MRI imaging and physician follow-up.

Results

After initiation on TMZ therapy as part of Stupp protocol, the patient experienced profound pancytopenia which prompted cessation of treatment on 10/28/2019 and required multiple subsequent platelet and Red Blood Cell (RBC) transfusions in addition to Filgrastim to augment recovery. After cell counts had fully recovered, Avastin/Optune treatment was started on 12/20/2019 with no further abnormalities noted on serial Complete Blood Count (CBC) testing. Outline of CBC data during treatment is outlined below (Graph 1 and 2). Serial Magnetic Resonance Imaging (MRI) with gadolinium contrast was utilized to surveil the size of lesion and associated vasogenic edema. Initial MRI was completed on 9/3/2019 after non-contrast Computed Tomography (CT) imaging of head demonstrated new intracranial lesion (Figure 1). This initial MRI demonstrated a 6.2 cm × 4.3 cm × 6.5 cm (transverse × anteroposterior × craniocaudal) heterogeneously contrast-enhancing lesion in the left frontal lobe extending to the right superior frontal gyrus and caudally to the anterior left thalamus. Extensive FLAIR signal representing vasogenic edema resulted in 9 mm of left-to-right midline shift at the level of the septum pellucidum. Stupp protocol simulation was conducted and radiotherapy began on 9/23/2019 along with TMZ. Radiotherapy ended on 11/4/2019 and MRI was repeated on 12/2/2019 which demonstrated a mild size increase compared to initial MRI with the lesion measuring 6.4 cm × 4.4 cm × 6.7 cm (Figure 2). More central necrosis was present on this MRI, overall FLAIR signal was mildly increased, and midline shift was stable. Avastin/Optune was started on 1/20/2020 and the MRI was repeated on 2/11/2020 which showed a decrease in the size of the lesion to 6.4 cm × 4.0 cm × 6.7 cm with decreased mass effect and

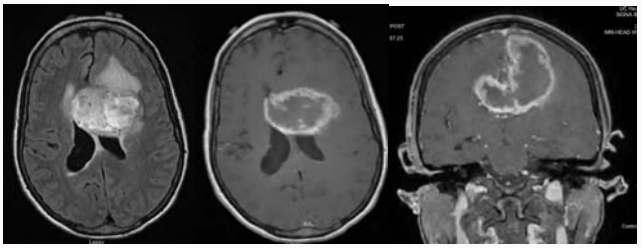


Figure 1: MRI dated 9/3/2019 demonstrating 6.5 × 4.3 × 6.5 cm (transverse × anteroposterior × craniocaudal) lesion. Sequences are (from left-to-right) axial T2 FLAIR, axial T1 post-contrast, coronal T1 post-contrast.

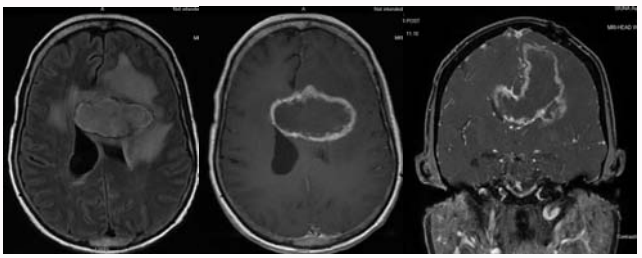


Figure 2: MRI dated 12/2/2019 demonstrating 6.4 × 4.4 × 6.7 cm (transverse × anteroposterior × craniocaudal) lesion. Sequences are (from left-to-right) axial T2 FLAIR, axial T1 post-contrast, coronal T1 post-contrast.

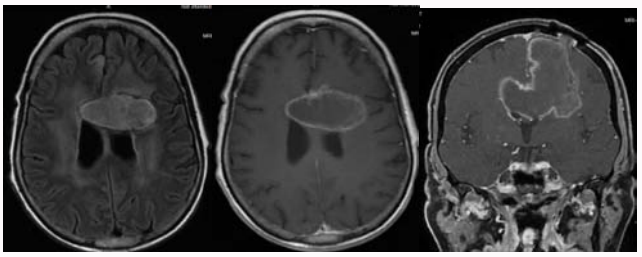


Figure 3: MRI dated 2/11/2020 demonstrating 5.6 cm × 3.5 cm × 6.0 cm (transverse × anteroposterior × craniocaudal) lesion. Sequences are (from left-to-right) axial T2 FLAIR, axial T1 post-contrast, coronal T1 post-contrast.

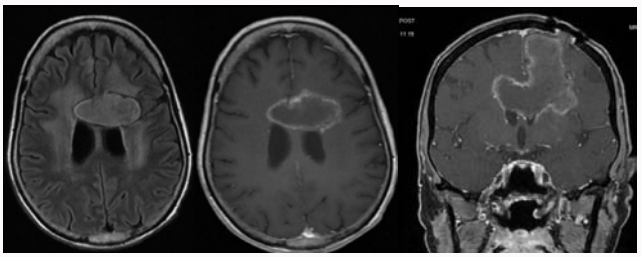


Figure 4: MRI dated 5/14/2020 demonstrating 5.3 cm × 3.1 cm × 5.8 cm (transverse × anteroposterior × craniocaudal) lesion. Sequences are (from left-to-right) axial T2 FLAIR, axial T1 post-contrast, coronal T1 post-contrast.

FLAIR signal (Figure 3), now with 4 mm of left-to-right midline shift at the septum pellucidum. MRI on 5/14/2020 again showed a slight decrease in the size of the lesion to 5.3 cm × 3.1 cm × 5.8 cm with improved perilesional FLAIR signal but increased T2 hyperintensity within the bilateral white matter (Figure 4), favored to represent radiation changes. Left-to-right midline shift was decreased on this study to 2 mm at the level of the septum pellucidum. Most recent MRI was obtained on 7/20/2020 which demonstrated overall stable lesion size at 5.7 cm × 3.2 cm × 5.5 cm (Figure 5). Morphology remained unchanged as did overall FLAIR signal and mass effect.

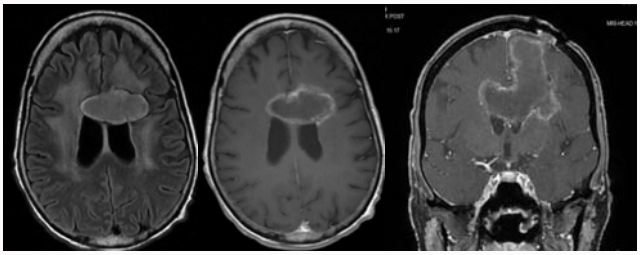
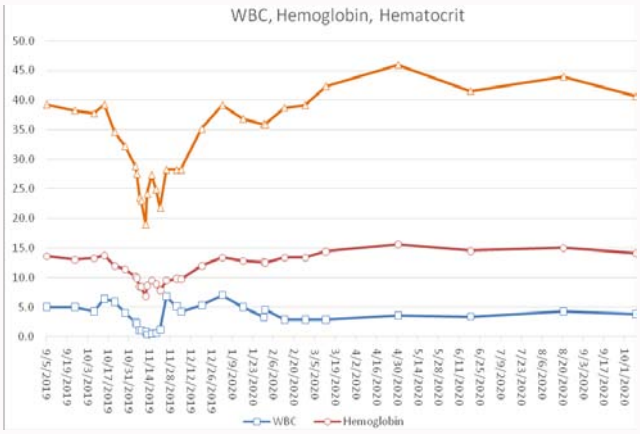
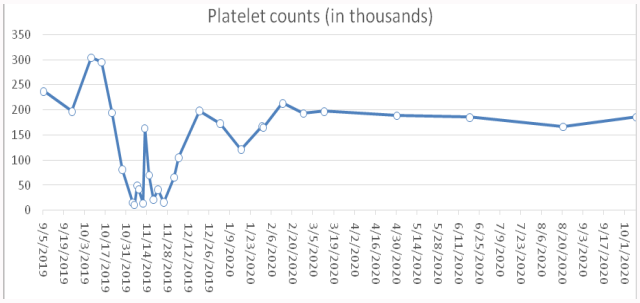


Figure 5: MRI dated 7/20/2020 demonstrating 5.7 cm × 3.2 cm × 5.5 cm (transverse × anteroposterior × craniocaudal) lesion. Sequences are (from left-to-right) axial T2 FLAIR, axial T1 post-contrast, coronal T1 post-contrast.



Graph 1: White blood count (WBC, in thousands), hemoglobin, and hematocrit counts during treatment. Vertical lines showing cessation of TMZ therapy on 10/20/2019 and initiation of Avastin/Optune therapy on 1/20/2020.



Graph 2: Platelet counts during treatment. Vertical lines showing cessation of TMZ therapy on 10/20/2019 and initiation of Avastin/Optune therapy on 1/20/2020.

Discussion

The combination of Bevacizumab and Optune device used for initial diagnosis has not been previously studied. Bevacizumab therapy is approved to treat adult patients with a GBM that has recurred. The efficacy of Bevacizumab therapy on its own has not shown to increase duration of over survival [3]. Bevacizumab targets angiogenesis and has displayed in previous studies a reduction in vascular permeability and edema, thereby reducing symptoms of the disease [4]. TTFs used by the Optune device has been FDA approved for adult patients with newly diagnosed GBM in the supra-tentorial region of the brain in conjunction with the Stupp protocol. Optune is also approved as a monotherapy in recurrent GBM in the supra-tentorial region of the brain. It is an anti-mitotic agent that disrupts glioblastoma cell division by delivering low intensity alternating electrical fields [5]. Optune has shown to increase progression free survival as well as overall survival, with minimal side effects [5]. The combination of Bevacizumab and Optune device has been previously studied in the recurrent setting. The combination of these modalities was thought to be effective, as the two therapies do not have overlapping side effects and they have two different treatment targets [6]. The safety of combining Bevacizumab and Optune has also been studied in the recurrent setting. The data indicates that using them together does not increase risk of stroke or hemorrhage, a side effect of Bevacizumab, nor does it increase the risk of skin toxicity, a known side effect of the Optune device [7]. Since our patient was unable to tolerate standard of care in the newly diagnosed setting, it was agreed upon to initiate treatment with the Optune device and Bevacizumab. The goal of combining the two therapies is to provide the benefits of both therapies while minimizing adverse side effects. In particular, the patient's bone marrow did not seem affected by this combination and she was able to continue with uninterrupted therapy.

Conclusion

The patient's scans remain stable with the combination of Bevacizumab and Optune device and her blood counts have returned to normal. We propose this combination of treatment may be beneficial when offered to patients with large or unresectable GBM tumors upfront, specifically those who are unable to tolerate TMZ due to allergy or those who experience adverse events from the drug.

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