Clinical Trials, Pathology and Case Studies

OMMEGA Publishers
Answering Intelligence

Case Report Open Access

Intravitreal Injection of Bevacizumab for Glioblastoma Multiforme Treatment: a Case Report

Donatella Sarti[1], Tiziana Melica[2], Stefano Luzi Fedeli[1], Giacomo Pellegrini[3], Caterina Fiorentini[1], Letterio Morabito[4], Stefano Guadagni[5], Giammaria Fiorentini[1*]

[1]Department of Oncology-Hematology, Azienda Ospedaliera "Ospedali Riuniti Marche Nord", 61122 Pesaro, Italy
[2]Department of Clinical Diagnostics, Azienda Ospedaliera "Ospedali Riuniti Marche Nord", 61122 Pesaro, Italy
[3]Department of Ophthalmology, Azienda Ospedaliera "Ospedali Riuniti Marche Nord", 61122 Pesaro, Italy
[4]Department of Neurosurgery, Azienda Ospedaliera "Ospedali Riuniti Marche Nord", 61122 Pesaro, Italy
[5]Department of Applied Clinical Sciences & Biotechnology, University of L'Aquila, 7100 L'Aquila, AQ, Italy, and Alma Mater Europaea – ECM, Slovenska ulica 17, Maribor, Slovenja

[*]**Corresponding author:** Dr. Giammaria Fiorentini, Department of Oncology-Hematology, Azienda Ospedaliera Ospedali Riuniti Marche Nord, Presidio Ospedaliero San Salvatore, via C. Lombroso 1, 62122 Pesaro, Italy, Tel: +39 0721364005; Fax +39 0721364094; E-mail: g.fiorentini@ospedalimarchenord.it

Abstract

Tumor angiogenesis depends on Vascular Endothelial Growth Factor (VEGF) secretion to promote neovascularization from existing vessels. In order to block this tumor-induced neo-angiogenesis, anti-VEGF antibody (bevacizumab) has been developed to bind and neutralize all biologically active iso-forms of VEGF). Bevacizumab (BV) is approved by Food and Drug Administration (FDA) for the treatment of recurrent Glioblastoma Multiforme (GBM), resulting in good tumor stability, in association with temozolomide (TMZ).

GBM is characterized by a poor prognosis and a median overall survival (OS) of 8- 16 months. There is currently no standard treatment options or approaches other than standard chemoradiation for patients with multifocal or single-lesion unresectable GBM.

In the current study, we present a case of tumor response after intravitreal injection of BV in a patient who progressed to chemoradiation with TMZ. This case report shows that the blockade of neo-angiogenesis by BV was able to induce tumor reduction and response to TMZ.

Keywords: Glioblastoma; Bevacizumab; Intravitreal injections; Tumor response

Received date: May 17, 2017
Accepted date: January 25, 2018
Published date: January 27, 2018

Citation: Sarti.D., et al. Intravitreal injection of bevacizumab for Glioblastoma Multiforme treatment: a case report. (2018) J Clin Trials Pathol Case Stud 3(1): 5- 7.

Introduction

The Central Nervous System (CNS) is formed by different cell types, including neurons, oligodendrocytes, and astrocytes. The transformation of theses cells results in neuroblastoma, oligodendroglioma, and astrocytoma, respectively. The astrocytoma grade IV, which is also known as Glioblastoma Multiforme (GBM), which is the most common primary adult brain tumor[1]. GBM is characterized by a poor prognosis, with a median overall survival (OS) between 8 and 16 months[2]. Poor prognosis is related also to the accumulation of CD4+CD25+-Foxp3+ regulatory T cells[3,4], which contribute to immunotherapeutic failure, and tumor progression.

Patients with multifocal or single-lesion unresectable GBM tumors have no standard treatment options or approaches other than standard chemo-radiation[5].

Current pharmacological treatment of GBM includes blood brain barrier-crossing chemotherapeutics, such as temozolomide (TMZ), and nitrosourea, vaccination against the Treg transcriptional regulator, and antibodies against Treg-associated cell surface molecules, (CD25, CTLA-4, and GITR)[1].

Surgical resection is the most used therapy for GBM, followed by chemo-radiation treatment with temozolomide (TMZ) and radiation, however, glioma cells often develop resistance to TMZ treatment[2].

Tumor cells need blood vessels to grow and diffuse to further metastatic sites. For this reason, they induce neo-vessel formation by increasing the vascular endothelial growth factor (VEGF). VEGF is a secreted mitogen that regulates angiogenesis in both normal and tumor growth[6]. Several studies show elevated levels of VEGF in the serum of patients with non–small cell lung, colorectal, breast, ovarian, uterine, and renal cancer[7]. Tumor angiogenesis depends on VEGF secretion to promote neovascularization from existing vessels. In order to block this tumor-induced neo-angiogenesis, anti-VEGF antibody (bevacizumab) has been developed to bind and neutralize all biologically active iso-forms of VEGF[8].

Bevacizumab (BV) was approved by the Food and Drug Administration (FDA) for treatment of recurrent GBM in 2009[9].

BV added to concurrent chemoradiation in an adjuvant setting (BV + 5-day TMZ and irinotecan), had moderate toxicity, and resulted in a median progression-free survival (PFS) of 14.2 months and median OS of 21.1 months[10]. Lou and colleagues reported that an upfront regimen of TMZ and BV for unresectable glioblastoma was well tolerated and provided a significant level of disease stabilization[11].

Reviewing the literature, it was observed that the use of intraocular administration of bevacizumab for the treatment of ocular metastases has been reported in breast and lung cancers and multiple myeloma[11-15], but never in GBM, where the bevacizumab was endovenously administered. The current study present a case of tumor response after intravitreal injection of BV in one patients failing chemoradiation with TMZ.

Case Report

The patient was a male of 78 years, with diagnosis of multiform glioblastoma, as emerged from the MRI, which showed an expansive lesion maily concentrated in the cortical frontal region of the left hemisphere. The GBM was K-ras (codons 12, 13) wild type. Primary tumor was surgically removed, and the hystological examination of the material attained from the surgical recision confirmed the diagnosis of GBM. A month after the surgery the magnetic resonance imaging (MRI) showed disease progression.

The patient received a cycle of TMZ (150 mg/mq/die x 5 days), followed by chemo-radiotherapy with TMZ combined to radiotherapy (5940 cGy, with fraction of 180 cGy7 day), and followed by TMZ of maintenance for 8 cycles (150 mg /mq /die x 5 days, repeated each 28 days). TMZ was then suspended and the patient continued the clinical follow up visits and MRI to monitor tumor response.

Tumor response, according to recist criteria v1.1, was partial response at the three months Follow-up, stable disease at 6 months and partial response at 12 months as showed by MRI, however at 20 months there was disease progression in multiple sites of the brain.

After consultation of radiotherapist and neurosurgeon, it was decided to start a palliative chemotherapy with TMZ (150 mg/mq/die x 5 days, repeated each 28 days). Tumor response after the 7th TMZ cycle was stable disease; hence TMS was continued for other three cycles, with a response of stable disease.

During this period the patient received also intravitreal injection of bevacizumab (1.25 mg in 0.05 ml) for the treatment of maculopathy, a concomitant disease suffered from the patient with sight reduction. The patient received a total of four intravitreal BV injections, the first one and the second one were done before the first cycle of TMZ, the third one was done after the second TMZ cycle, and the fourth was done after the fourth TMZ cycle.

MRI evaluation after the fourth cycle of TMZ and BV intravitreal showed partial response, for this reason TMZ was continued. Tumor response after the seventh TMZ cycle was stable disease; hence TMZ was continued for other 4 cycles. The MRI evaluation at the end of TMZ therapy showed disease progression.

Conclusion

BV is an Anti-angiogenic factor that inhibits VEGF and is able to cross the blood brain barrier. For this reason it is often used as intravitreal route of administration for the treatment of ocular metastases, by reducing neo-vessel formation in the metastases. Intravitreal administration of bevacizumab results in good tumor control of iris metastases from breast cancer[12].

BV has been also approved by the FDA for treatment of recurrent GBM and has shown good results with low level of toxicity for the treatment of recurrent GMB[9]. Our patient was firstly treated with chemo-radiation for GMB, and after disease progression with TMZ. It is quite rare, generally, to obtain any kind of response after failing radiotherapy associated to TMZ.

In that period the literature showed the utility of BV for GMB because of its anti-angiogenetic effect. The eye is anatomically correlated with the brain and the drug intravitreal administered are able to cross the blood brain barrier. Chemotherapy was given in concomitant with intravitreal BV injections for the treatment of maculopathy. The association BV and TMZ showed partial response after 6 month of therapy, and progression free survival (PFS) of 11 months.

Lou and colleagues reported that TMZ and BV given intravenously for unresectable glioblastoma was well tolerated and provided a significant level of disease stabilization[5]. We observed similar results in our case with a disease improvement observed during concomitant treatment with TMZ and low doses of intravitreal BV. The GMB was K-ras (codons 12, 13) wild type, for these reasons, we hypothesize that the improvement was depending to the synergism of TMZ and the anti-angiogenic effect of BV. This is of particular interest because we used low doses of BV, resulting in a significant tumor response in a case where the TMZ alone would not have been useful after disease recurrence. This case report shows that the blockade of neo-angiogenesis by BV was able to improve tumor reduction and response to TMZ.

We hypothesize that this way of administration (intravitreal) should be carefully evaluated in further clinical trials with more patients.

References

1. Wainwright, D.A., Dey, M., Chang, A., et al. Targeting Tregs in Malignant Brain Cancer: Overcoming IDO. (2013) Front Immunol 4: 116.
Pubmed | Crossref | Others

2. Stupp, R., Mason, W. P., Van Den Bent, M. J., et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. (2005) N. Engl. J. Med 352: 987–996
Pubmed | Crossref | Others

3. El Andaloussi, A., Han, Y., Lesniak, M.S. Prolongation of survival following depletion of CD4CCD25C regulatory T cells in mice with experimental brain tumors. (2006) J. Neurosurg 105(3): 430–437.
Pubmed | Crossref | Others

4. Fecci, P.E., Mitchell, D.A., Whitesides, J.F., et al. Increased regulatory T-cell fraction amidst a diminished CD4 compartment explains cellular immune defects in patients with malignant glioma. (2006) Cancer Res 66(6): 3294–3302.
Pubmed | Crossref | Others

5. Lou, E., Peters, K.B., Sumrall, A.L., et al. Phase II trial of upfront bevacizumab and temozolomide for unresectable or multifocal glioblastoma. (2013) Cancer Med 2(2): 185-95.
Pubmed | Crossref | Others

6. Lal, B.K., Varma, S., Pappas, P.J., et al. VEGF increases permeability of the endothelial cell monolayer by activation of PKB/akt, endothelial nitric-oxide synthase, and MAP kinase pathways. (2001) Microvasc Res 62: 252-62.
Pubmed | Crossref | Others

7. Rini, B.I., Rathmell, W.K. Biological aspects and binding strategies of vascular endothelial growth factor in renal cell carcinoma. (2007) Clin Cancer Res 13(2 Pt 2): 741s-746s.
Pubmed | Crossref | Others

8. Gerber, H.P., Ferrara, N. Pharmacology and pharmacodynamics of bevacizumab as monotherapy or in combination with cytotoxic therapy in preclinical studies. (2005) CancerRes 65(3): 671-680.
Pubmed | Crossref | Others

9. Cohen, M.H., Shen, Y.L., Keegan, P., et al. FDA drug approval summary: bevacizumab (Avastin) as treatment of recurrent glioblastoma multiforme. (2009) Oncologist 14(11): 1131–1138.
Pubmed | Crossref | Others

10. Vredenburgh, J.J., Desjardins, A., Reardon, D.A., et al. The addition of bevacizumab to standard radiation therapy and temozolomide followed by bevacizumab, temozolomide, and irinotecan for newly diagnosed glioblastoma. (2011) Clin. Cancer Res 17: 4119–4124.
Pubmed | Crossref | Others

11. Pierson, T.M., Tebit, E.V., El Sayed, A., et al. Orbital Metastases from Breast Cancer: Retrospective Analysis at an Academic Cancer Center. (2016). Breast J 22(4): 447-450.
Pubmed | Crossref | Others

12. Seidman, C.J., Finger, P.T., Silverman, J.S., et al. Intravitreal bevacizumab in the management of breast cancer iris metastasis. (2017) Retin Cases Brief Rep 11(1): 47-50.
Pubmed | Crossref | Others

13. Augustine, H., Munro, M., Adatia, F., et al. Treatment of ocular metastasis with anti-VEGF: a literature review and case report. (2014) Can J Ophthalmol 49(5): 458-463.
Pubmed | Crossref | Others

14. Zhou, Q., Liang, J., Lu, H. Intravitreal bevacizumab for ocular metastasis of multiple myeloma. (2013) Optom Vis Sci. 90(9): e236-40.
Pubmed | Crossref | Others

15. el Filali, M., Ly, L.V., Luyten, G.P., et al. Bevacizumab and intraocular tumors: an intriguing paradox. (2012) Mol Vis. 18: 2454-67.
Pubmed | Crossref | Others