Bevacizumab for glioblastoma

- Molecular Correlates of Long-Term Response to Bevacizumab in Glioblastoma
- First-in-human phase 1 study of KHK2455 monotherapy and in combination with mogamulizumab in patients with advanced solid tumors
- Efficacy and safety of combining re-irradiation with bevacizumab compared to bevacizumab alone in the management of recurrent high-grade gliomas: a meta-analysis and systematic review
- Multimodal nanoparticles co-delivering bevacizumab and dichloroacetate for dual targeting of neoangiogenesis and hyperglycolysis in glioblastoma treatment
- Comparative safety analysis of bevacizumab and alkylating agent in glioblastoma management - What have we learned recently?
- Spinal cord metastasis in a long-term survivor of primary malignant glioblastoma: A case report
- Hemorrhagic and ischemic risks of anti-VEGF therapies in glioblastoma
- Treatment mechanism and research progress of bevacizumab for glioblastoma

Over the past decade, further advances have been achieved in various disciplines, most prominently including antiangiogenic treatment with bevacizumab. Still, whether these therapeutic innovations have translated to the general population remains unclear.

Patients with glioblastoma multiforme (GBM) that are cancer stem cell positive (GSC [+]) essentially cannot benefit from antiangiogenic therapy. In a study, the potential anti-angiogenic and anti-invasive effects of Olea europaea (olive) leaf extract (OLE) were tested using GSC (+) tumours. OLE (2mg/mL) caused a significant reduction in tumour weight, vascularisation, invasiveness and migration ($p=0.0001$, $p<0.001$, $p=0.004$; respectively) that was associated with reducing the expression of VEGFA, MMP-2 and MMP-9. This effect was synergistically increased in combination with bevacizumab. Therefore, current findings may contribute to research on drugs that inhibit the invasiveness of GBM [1)].

Results indicate that the local intracerebral microinfusion of antiangiogenic compounds is an effective way to overcome the logistical problems of inhibiting glioma-induced angiogenesis [2)].

Angiopoietin 1/ angiopoietin 2 balance has prognostic value in patients with primary glioblastomas (GBMs). This findings support the need for further studies of the feasibility of antiangiogenic therapy in primary GBMs, with a special focus on the normalization of tumor vasculature [3)].

A study was designed to define the malignant glioma cases most suitable for antiangiogenic therapy and to demonstrate the efficacy of anti-angiogenic therapy using soluble-form Flt1 (sFlt1) gene delivery in mice. In human malignant glioma samples (39 glioblastomas, 21 anaplastic astrocytomas and 4 anaplastic oligoastrocytomas), protein expression of VEGF, and its specific natural inhibitor, sFlt1, as well as vessel architecture were assessed. Among these variables, VEGF >1000 ng/ml,

VEGF/sFlt1 ratio >1, vessel density >30, and vessel area >7% were prognostic factors for malignant gliomas. VEGF/sFlt1 ratio >1 was the most powerful prognostic marker for survival in multivariate analysis. The sFlt1 gene was also successfully introduced into U87 glioma cells in vitro, resulting in 31% tumor growth inhibition in vivo. sFlt1-transfected tumor demonstrated high sFlt-1 expression along with diminished vessel density and area compared with the control tumor. In transfected tumor, VEGF expression was decreased in the viable area, but still high in the hypoxic area. sFlt1 and VEGF expression was re-evaluated in vitro using glioma cells under normoxic and hypoxic conditions. For sFlt1-transfected cells, VEGF expression was upregulated, but sFlt1 expression was downregulated, resulting in an increase of VEGF/sFlt1 ratio in hypoxic conditions.

Malignant gliomas with a high VEGF/sFlt1 ratio and large vessel area are good candidates for anti-angiogenic therapy. Soluble Flt1 gene delivery was demonstrated to inhibit glioma growth, but this was limited in hypoxic areas [4)].

Currently, standard therapy incorporating surgery, cranial irradiation, and temozolomide chemotherapy is uniformly applied for all patients. With this approach, median survival remains unacceptably poor including fewer than 10% of patients surviving 5 years after diagnosis. Salvage therapies are ineffective with PFS-6 rates under 10% for non-bevacizumab regimens and 40% for bevacizumab. Furthermore, all patients ultimately progress on bevacizumab, and then typically die from rapidly progressive tumor. Innovative treatment strategies directed to distinct patient subsets defined by specific genetic and gene expression analyses represent an attractive therapeutic paradigm shift for this highly challenging complex tumor, offering promise to ultimately improve outcome [5)].

Despite the rapid incorporation of the current standard treatment in clinical practice and the thereby achieved modest survival gain at the population-level, prevailing pattern of care (POC)needs to be reconsidered and standardized, especially for elderly glioblastoma patients who bear a large disease burden and carry the worst prognosis. Future POC studies are urgently needed and would benefit from the systematic inclusion of quality-of-life data and molecular tumor markers, so that this information could be captured in population-based cancer registries [6)].

Indications

Bevacizumab for glioblastoma recurrence

see Bevacizumab for glioblastoma recurrence.

Bevacizumab for newly diagnosed glioblastoma

see Bevacizumab for newly diagnosed glioblastoma

1)
Tezcan G, Taskapilioglu MO, Tunca B, Bekar A, Demirci H, Kocaeli H, Aksoy SA, Egeli U, Cecener G, Tolunay S. Olea europaea leaf extract and bevacizumab synergistically exhibit beneficial efficacy upon human glioblastoma cancer stem cells through reducing angiogenesis and invasion in vitro.

Biomed Pharmacother. 2017 Apr 15;90:713-723. doi: 10.1016/j.biopha.2017.04.022. [Epub ahead of print] PubMed PMID: 28419967.
2)

Schmidt NO, Ziu M, Carrabba G, Giussani C, Bello L, Sun Y, Schmidt K, Albert M, Black PM, Carroll RS. Antiangiogenic therapy by local intracerebral microinfusion improves treatment efficiency and survival in an orthotopic human glioblastoma model. Clin Cancer Res. 2004 Feb 15;10(4):1255-62. PubMed PMID: 14977823.
3)

Sie M, Wagemakers M, Molema G, Mooij JJ, de Bont ES, den Dunnen WF. The angiopoietin 1/angiopoietin 2 balance as a prognostic marker in primary glioblastoma multiforme. J Neurosurg. 2009 Jan;110(1):147-55. doi: 10.3171/2008.6.17612. PubMed PMID: 18991494.
4)

Takano S, Ishikawa E, Matsuda M, Sakamoto N, Akutsu H, Yamamoto T, Matsumura A. The anti-angiogenic role of soluble-form VEGF receptor in malignant gliomas. Int J Oncol. 2016 Dec 19. doi: 10.3892/ijo.2016.3810. [Epub ahead of print] PubMed PMID: 28000842.
5)

Reardon DA, Ligon KL, Chiocca EA, Wen PY. One size should not fit all: advancing toward personalized glioblastoma therapy. Discov Med. 2015 Jun;19(107):471-477. PubMed PMID: 26175405.
6)

Woehrer A, Bauchet L, Barnholtz-Sloan JS. Glioblastoma survival: has it improved? Evidence from population-based studies. Curr Opin Neurol. 2014 Dec;27(6):666-74. doi: 10.1097/WCO.0000000000000144. PubMed PMID: 25364955.