Q&A: Understanding glioblastoma (GBM)

BY JOHN DE GROOT, M.D.

Ever heard of gliomas? These primary brain tumors arise within the brain, but we don't know the cell of origin.

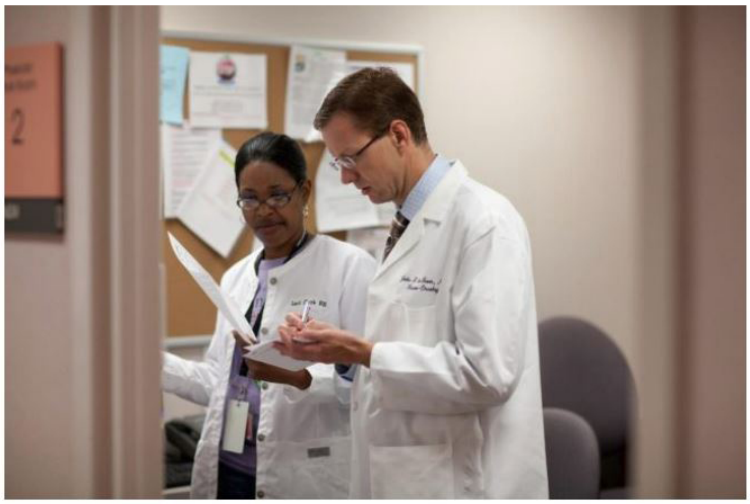
There are multiple grades of gliomas -- grade 2, 3 and 4, with grade 4 being the most malignant.

Glioblastoma, sometimes referred to as glioblastoma multiforme (GBM), is considered a grade 4 tumor. They are the most aggressive and are very infiltrative -- they spread into other parts of the brain quickly. Glioblastomas don't metastasize (or spread) outside of the brain.

Glioblastomas can occur in any lobe of the brain and even the brain stem and cerebellum, but more commonly occur in the frontal and temporal lobes. Below, I've answered some common questions I get about glioblastoma.

1. Are there any known causes or risks factors for glioblastoma?
Glioblastoma are more common in males, persons older than 50, and people of Caucasian or Asian ethnicity.

There are a few very rare familial syndromes that are associated with brain tumors. One of the only known risk factors that we have for brain tumors is radiation exposure.



John de Groot, M.D. (right), with a colleague

> Glioblastomas can occur in any lobe of the brain and even the

Brain and spinal cord tumor grades

Some brain and spinal cord tumors are more likely to grow into nearby tissues (and to grow quickly) than are other tumors. The World Health Organization (WHO) divides brain and spinal cord tumors into 4 grades (using Roman numerals I to IV), based largely on how the cells look under the microscope:

- **Grade I:** These tumors typically grow slowly and do not grow into (invade or infiltrate) nearby tissues. They can often be cured with surgery.
- **Grade II:** These tumors also tend to grow slowly but they can grow into nearby brain tissue. They are more likely to come back after surgery than grade I tumors. They are also more likely to become faster-growing tumors over time.
- **Grade III:** These tumors look more abnormal under the microscope. They can grow into nearby brain tissue and are more likely to need other treatments in addition to surgery.
- **Grade IV:** These are the fastest growing tumors. They generally require the most aggressive treatment.

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Surgical and Non-Surgical Management and Treatment of Glioblastoma: II. Recurring Tumors

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Abstract

Glioblastoma (also known as glioblastoma multiform) is the most common primary brain tumor in adults. It remains an unmet need in oncology. Complementing an earlier discussion of primary and secondary tumors in both cases of monotherapies and combined therapies, Clinical trials and other reported practices will also be discussed and summarized. Regarding chemotherapy, whereas it has historically provided little durable benefit with tumors recurring within several months, for brain tumors, the access is hindered or even forbidden by the presence of the brain protective barriers, chiefly the blood brain barrier. More effective therapies involving other options are required including surgery, conformal radiotherapy, boron neutron therapy, intensity modulated proton beam therapy, antiangiogenic therapy, alternating electric field therapy, ...without neglecting palliative therapies. Research conducted in these and other options is also reviewed to include microRNA, immunotherapy, adjuvant therapy, gene therapy, stem cell therapy, and intra-nasal drug delivery.

Abbreviations: BBB: Blood Brain Barrier; BPB: Brain Protective Barriers; DC: Dendritic Cells; EGFR: Epidermal Growth Factor Receptor gene (a pro-angiogenic cytokine); EMA: European Medicines Agency; FDA: (U.S.) Food & Drug Administration; GB: GlioBlastoma; GBM: GlioBlastoma Multiform; GBSLC: GB Stem-Like Cells; GDV: Gene Delivery Vehicle; GTT: Gene Transfer Technology; INDD: Intra-Nasal Drug Delivery; KPS: Karnofsky Performance Score; MGMT: O6-alkylguanine DNA alkyltransferase; OS: Overall Survival; PET: Positron Emission Tomography; RNA: Ribo-Nucleic Acid; TMZ: Temozolomide (an alkalyting agent used as a treatment of some brain cancers; as a first-line treatment for GBs and as a second-line treatment for astrocytomas) (brand names: Temodar, Temodal and Temcad); TSC: Tumor Stem Cell

Disorders cited: Asthenia; Convulsions; Diarrhea; Fatigue; Fibrosis (renal, hepatic, pulmonary); Glioblastoma; Glioblastoma Multiform; Hematologic Toxicity; Hypertension; Leucopenia;Lymphopenia; Malaria; Migraine; Radionecrosis; Rash; Recurrent Glioblastoma; Skin toxicity; Thrombocytopenia; Thromboembolic events

Drugs mentioned: Afatinib (an irreversible inhibitor of mutated EGFR); Aflibercept; 5-Aminolevulinic Acid (a surgery dye); Antiangiogenics; Bevacizumab (a monoclonal antibody with activity against VEVF); Carboplatin; Carmustine; Cediranib (an angiogenic inhibitor); Celecoxib; Cetuximab; Cilengitide (an inhibitor of integrin αVβ3 and αVβ5); Corticosteroids (including anti-convulsant ones); Cytarabine; Entemustine; Enzasturine; Epidermal Growth Factor Receptor; Ertolinib; Etoposide; Everolimus; Farnesyl transferse antagonist; Fotemustine; Gefitinib; Histone deacetylase antagonist; Irinotecan; Lapatinib (HKI-272); Lomustine; Nimustine; Nitrosoureas; Nivolumab (Opdivo); O6-benzylguanine (agent that induces MGMT depletion); Pembrolizumab (Keytruda); Perillyl Alcohol; Phospholinositide 3-kinase antagonist; Polifeprosan; Procarbazine; Sirolimus (an inhibitor of MTOR) (mammalian target of Rapamycin); Statins; Steroids; Temozolomide; Vincristine.

Keywords: Antiangiogenic Therapy; Bevacizumab; Blood Brain Barrier; Cediranib; Cilengitide; Epidermal Growth Factor Receptor; Glioblastoma; Glioblastoma Multiform; Gliomatosis; MGMT Methylation; Recurrent Glioblastoma; Stem-Like Cancer Cells; Surgery; Temozolomide.

Introduction

Glioblastoma (also known as glioblastoma multiform) is the most common primary brain tumor in adults. It remains an unmet need in oncology. Figure 1 is a colored positron emission tomography of the brain showing a GB. In a companion article [1], I limited my considerations to primary and secondary tumors and their metastases. I discussed at some length the standard treatment of glioblastoma (GB) consisting of

a. surgery (maximal resection of ~/> 98% of the tumor) followed by

b. radio chemotherapy (6 weeks of radiotherapy at a dose of 60 Grey [Gy] together with concomitant chemotherapy with Temozolomide (TMZ) at a rate of 75 mg/m² daily); and once chemoradiotherapy is complete

c. Adjuvant treatment (a minimum of 6 months with TMZ starting at a dose of 150-200 mg/m2 for 5 days every 28 days). Chemotherapy by itself that is the use of cytotoxic drugs in isolation or in combination with other drugs, has historically provided little durable benefit as the tumors

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Medical Care

The treatment of glioblastomas remains difficult in that no contemporary treatments are curative.[23] While overall mortality rates remain high, recent work leading to an understanding of the molecular mechanisms and gene mutations combined with clinical trials are leading to more promising and tailored therapeutic approaches. Multiple challenges remain, including tumor heterogeneity, tumor location in a region where it is beyond the reach of local control, and rapid, aggressive tumor relapse. Therefore, the treatment of patients with malignant gliomas still remains palliative and encompasses surgery, radiotherapy, and chemotherapy. See Brain Cancer Treatment Protocols for summarized information.

Upon initial diagnosis of glioblastoma multiforme (GBM), standard treatment consists of maximal surgical resection, radiotherapy, and concomitant and adjuvant chemotherapy with temozolomide.[24, 25] For patients older than 70 years, less aggressive therapy is sometimes employed, using radiation or temozolomide alone.[26, 27, 28] A study by Scott et al found that elderly patients with glioblastoma who underwent radiotherapy had improved cancer-specific survival and overall survival compared with those who did not undergo radiotherapy treatment.[29]

Initial means just that, NOT A FULL MONTH after diagnosis. DELAY only allows the aggreesive tumor to spread which greatly reduces odds of a successful and life-saving outcome.