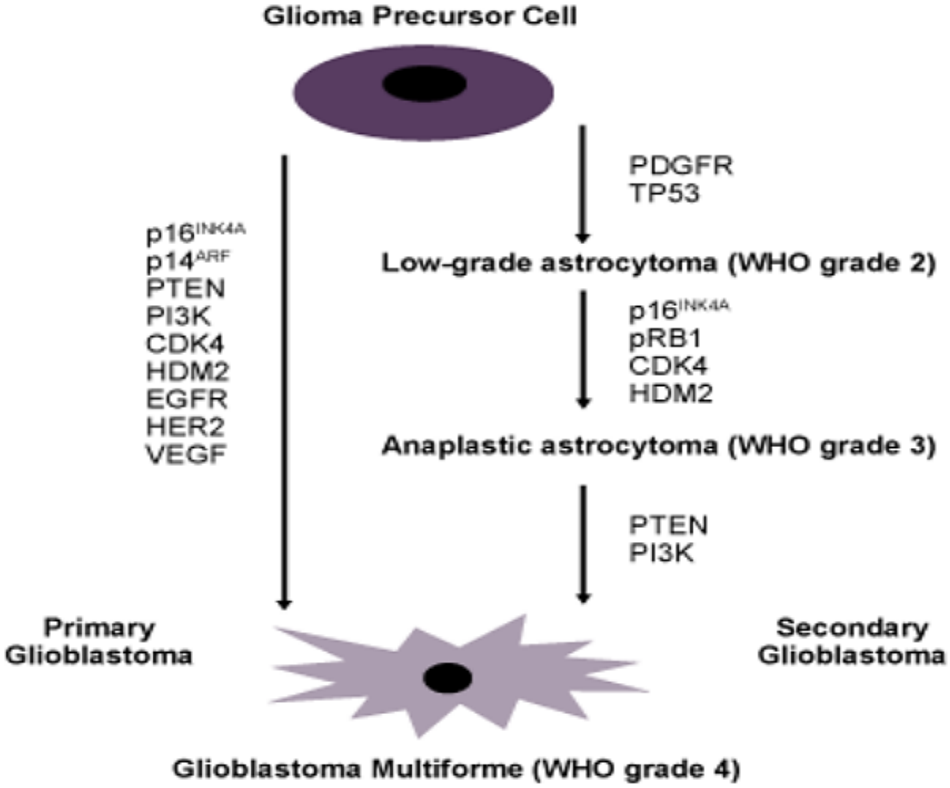
GLIOBLASTOMA MULTIFORME (GBM)

Background

- The incidence of GBM is 3.1 per 100,000 per year.
- It accounts for 12% to 15% of intracranial tumors and 50% to 60% of all primary brain tumors with a median age at glioblastoma diagnosis of 63 years.
- There is more predilection for males.
- Median survival for patients with GBM is <12 months, particularly in elder patients.

Genetic alterations in primary and secondary GBM:

- GBM is a genetically heterogeneous disease.
- Two subgroups of glioblastomas have been described.
  - Primary or de novo (more than 90% of GBMs) i.e., without an antecedent lower-grade tumor.
  - Secondary GBMs (10%) developed following a transformation from lower-grade gliomas (WHO grade 2/3).
- Transcriptional profiling has demonstrated common and differential gene expression between primary and secondary GBM.



Initial Workup

- **Clinical assessment including:**
  - General examination and
  - Neurological examination.
- **Pathology review.**
- **Laboratory Investigations:**
  - Full blood and
  - Biochemistry profiles.
- **MRI brain.**

Treatment

I. Early disease

- Surgical treatment under the care of neurosurgical services.

- Combined Radiation Therapy and Chemotherapy under radiation therapy services.

- Radiation therapy treated to 60 Gy over 6 weeks and
- Daily Temozolomide at 75 mg/m^2/day followed by
- 6 cycles of monthly Temozolomide at a dose of 150-200 mg/m^2/day for 5 days out of 28 days.
  N.B. This modality of treatment will be under our radiotherapy staff so any radiation dose modification will be based on their judgment.

II. Recurrent, advanced, or irresectable GBM

- These Patients who underwent surgery and radiotherapy at progression may be considered for one of the following options under our unit at the medical oncology department.

Temozolomide

Indications:

- Treatment of adult patients with refractory anaplastic astrocytoma, i.e., patients who experienced disease progression on a drug regimen containing a nitrosourea and procarbazine at first relapse.
- Treatment of patients with newly diagnosed high-grade gliomas concomitantly with radiotherapy and then as adjuvant treatment.
- Conventional temozolomide is given as 150-200 mg/ m^2 5 days of each 28-day cycle

Bevacizumab

Indication:

- Treatment of glioblastoma with progressive disease following prior therapy
- Bevacizumab is used as a single agent or in combination with temozolomide.

Irinotecan
• Used in the setting of second line usually supplementing Bevacizumab

Other treatment modalities:

- Gama knife for selected cases.
- Best supportive care.
- Anti-epileptic therapy will be offered for those who develop seizures as and can be considered pre-operatively.

Treatment Schedules

Bevacizumab
• Single-agent Bevacizumab: 10 mg/kg every 2 weeks.
Combination of Bevacizumab and Temozolomide (TMZ)
• TMZ: 150 – 200 mg/m^2 orally daily on days 1-5 of each 4-week cycle. • Bevacizumab: 10mg/kg IV q2w.
Combination of Bevacizumab and Irinotecan
• Bevacizumab: 10 mg/kg • Irinotecan: 125 mg/m^2 every 2 weeks. • The dose of Irinotecan is based on the patient's anticonvulsant treatment. • Patients taking enzyme-inducing antiepileptic drugs (EIAEDs) will increase the dose to 340 mg/m^2.

Follow Up Protocol

- Brain MRI 2 – 6 weeks after finishing RT then
  - Every 2 – 4 months for 3 years then
  - Every 6 months indefinitely.

References

1) Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med. 2005;352:987-996.
2) Stupp R, Hegi ME, Mason WP, et al. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomized phase III study: 5-year analysis of the EORTC-NCIC trial. Lancet Oncol. 2009;10:459-466.
3) Vredenburgh JJ, Desjardins A, Herndon JE, et al. Bevacizumab plus irinotecan in recurrent glioblastoma multiforme. J Clin Oncol. 2007;25:4722-4729.
4) Stark-Vance V. Bevacizumab and CPT-11 in the treatment of relapsed malignant glioma. NeuroOncol. 2005;7:369.
5) Vredenburgh JJ, Desjardins A, Herndon JE, et al. Phase II trial of bevacizumab and irinotecan in recurrent malignant glioma. Clin Cancer Res. 2007;13:1253-1259.
6) Hasselbalch B, Lassen U, Grunnet K, et al. Bevacizumab, a monoclonal antibody to thevascular endothelial growth factor (VEGF), and irinotecan for treatment of recurrent primary brain tumors in adults. NeuroOncol. 2007;9:514.
7) Kang TY, Jin T, Elinzano H, et al. Irinotecan and bevacizumab in progressive primary brain tumors, an evaluation of efficacy and safety. J Neurooncol. 2008;89:113-118.
8) Norden AD, Young GS, Setayesh K, et al. Bevacizumab for recurrent malignant gliomas: Efficacy, toxicity, and patterns of recurrence. Neurology. 2008;70:779-787.
9) Bokstein F, Shpigel S, Blumenthal DT. Treatment with bevacizumab and irinotecan for recurrent high-grade glial tumors. Cancer. 2008;112:2267-2273.
10) Friedman HS, Prados MD, Wen PY, et el. Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. J ClinOncol. 2009;27:4733-4740.
11) Cloughesy TF, Prados MD, Wen PY, et al. A phase II, randomized, non-comparative clinical trial of the effect of bevacizumab (BV) alone or in combination with irinotecan (CPT) on 6-month progression free survival (PFS6) in recurrent, treatment-refractory glioblastoma (GBM). Program and abstracts of the 44th Annual Meeting for the American Society of Clinical Oncology; May 30 - June 3, 2008; Chicago, Illinois. Abstract 2010b.
12) Brada M, Hoang-Xuan K, Rampling R, et al. Multicenter phase II trial of temozolomide in patients with glioblastomamultiforme at first relapse. Ann Oncol. 2001;12:259-266.
13) Brandes AA, Ermani M, Basso U, et al. Temozolomide as a second-line systemic regimen in recurrent high-grade glioma: a phase II study. Ann Oncol. 2001;12:255-257.
14) Yung WK, Albright RE, Olson J, et al. A phase II study of temozolomide vs. procarbazine in patients with glioblastomamultiforme at first relapse. Br J Cancer. 2000;83:588-593.
15) Perry JR, Rizek P, Cashman R, et al. Temozolomiderechallenge in recurrent malignant glioma by using a continuous temozolomide schedule: the "rescue" approach. Cancer. 2008;15;113:2152-2157.