Cerebral Glioblastoma Multiforme Diagnosis and Management

By
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Anatomy of human Brain

- Cerebrum
- Cerebellum
- Spinal cord
- Choroid plexus
- Ventricle
- Cerebrum
- Hypothalamus
- Optic nerve
- Pituitary gland
- Pons
- Medulla
Classification of CNS tumors by site

- Meninges: 25.8%
- Temporal lobe: 9.0%
- Frontal lobe: 12.7%
- Parietal lobe: 6.7%
- Occipital lobe: 1.9%
- Cerebrum: 2.6%
- Cerebellum: 3.9%
- Ventricle: 1.4%
- Brain stem: 2.2%
- Other Brain: 15.4%
- Other CNS: 0.8%
- Spinal Cord & Cauda Equina: 3.9%
- Cranial Nerves: 5.8%
Glioblastoma multiforme (GBM) is the most common primary central nervous (CNS) tumor in adults comprising approximately 50% of all primary intracranial tumors. They generally occur in the fifth and sixth decades of life.
Most common histology in CNS tumors according to age

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Most Common Histology</th>
<th>Second Most Common Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4</td>
<td>Embryonal/primitive/medulloblastoma</td>
<td>Pilocytic astrocytoma</td>
</tr>
<tr>
<td>5-9</td>
<td>Pilocytic astrocytoma</td>
<td>Embryonal/primitive/medulloblastoma</td>
</tr>
<tr>
<td>10-14</td>
<td>Pilocytic astrocytoma</td>
<td>Embryonal/primitive/medulloblastoma</td>
</tr>
<tr>
<td>15-19</td>
<td>Pilocytic astrocytoma</td>
<td>Pituitary</td>
</tr>
<tr>
<td>20-34</td>
<td>Pituitary</td>
<td>Meningioma</td>
</tr>
<tr>
<td>35-44</td>
<td>Meningioma</td>
<td>Nerve Sheath</td>
</tr>
<tr>
<td>45-54</td>
<td>Meningioma</td>
<td>Glioblastoma</td>
</tr>
<tr>
<td>55-64</td>
<td>Meningioma</td>
<td>Glioblastoma</td>
</tr>
<tr>
<td>65-74</td>
<td>Meningioma</td>
<td>Glioblastoma</td>
</tr>
<tr>
<td>75-84</td>
<td>Meningioma</td>
<td>Glioblastoma</td>
</tr>
<tr>
<td>85+</td>
<td>Meningioma</td>
<td>Glioblastoma</td>
</tr>
</tbody>
</table>
Histopathology and molecular correlation

Diffuse, fibrillary astrocytomas are the most common type of primary brain tumor in adults. These tumors are divided histopathologically into three grades of malignancy: World Health Organization (WHO) grade II diffuse astrocytoma, WHO grade III anaplastic astrocytoma, and WHO grade IV Glioblastoma.
Molecular origin

Regulation of p53 and pRb function.

p14 and p16 function is inactivated in more than half of Glioblastoma, as well as in a significant fraction of grade III (anaplastic) astrocytoma, due to homozygous deletion of a DNA sequence at chromosomal location 9p21 that encodes each of these tumor suppressors.
Formation of GBM

Differentiated Astrocytes or Precursor Cells

- EGFR gene amplification or overexpression
- MDM2 gene amplification or overexpression
- LOH 9p (p15, p16)
- LOH 10 (PTEN)

Low-Grade Astrocytoma WHO Grade II

- LOH 17p/p53 mutation
- PDGF A-chain overexpression
- PDGF-α receptor overexpression
- LOH 22q

2–10 years

Anaplastic Astrocytoma WHO Grade III

- LOH 13q/RB1 mutation
- LOH 19q
- LOH 9q (p15, p16)

2–3 years

Primary GBM WHO Grade IV

Secondary GBM WHO Grade IV

- LOH 10 p and q
- PDGF-α amplification
- DCC loss of expression

9–12 months
Common Adult Tumors Frequent Gene and Chromosomal Alterations:

Grade II astrocytoma: TP53

Grade III anaplastic astrocytoma: TP53-**MDM2** **CDKN2A-CDK4-RB**

Grade IV glioblastoma: TP53b-**MDM2** **CDKN2A-CDK4-RB** **EGFR**c, **PTEN**

Grade II oligodendroglioma: Chromosome 1p-19q translocations

Grade III oligodendroglioma: Chromosome 1p-19q translocations Meningioma NF2
Brain tumors can cause any type of psychiatric symptoms. Rarely, brain tumors can present without any localizing signs but with psychiatric symptoms.

A review of the literature indicates that there is no association between psychiatric symptoms and tumor location or histological type.

Hence, it is important for clinicians to have an index of suspicion of brain tumor in patients with new-onset psychiatric symptoms, atypical presentations and treatment resistance and, as a result, consider neuroimaging.

Early detection is of paramount importance for treatment and quality of life of patients.

*Expert Rev Neurother. 2007 Apr;7(4):343-9*
Symptoms:

1- Related to increase intracranial pressure
2- Related to tumor site
3- Others
Brain edema in Mets vs brain edema in GBM

Fig. 1. Axial T2-weighted MR image showing the typical aspect of edema in cerebral metastases in a patient with pulmonary carcinoma.

Source: Neurosurg Focus © 2007 American Association of Neurological Surgeons

Fig. 2. Axial T2-weighted MR image showing cerebral edema in a patient with GBM.

Source: Neurosurg Focus © 2007 American Association of Neurological Surgeons
staging and risk assessment

- Staging includes imaging of the brain, ideally with magnetic resonance imaging (MRI).
- Lumbar puncture is generally not necessary,

ESMO Recommendations 2008
TNM staging

- The AJCC system is based on GTM classification (G=grade, T=size, M=metastases).
- T stage is subdivided into supra tentorial and infra tentorial location.
- It's also classified into five staging groups (clinical-diagnostic, surgical evaluative, post-surgical resection-pathologic, re-treatment and autopsy).
- N staging is irrelevant.
- G classification has prognostic value: G1 through G3 represents stages from well to poorly differentiated tumors cytology, G4 adds features of pleomorphism and necrosis and corresponds to Glioblastoma multiforme.
Treatment Plan

What is the target???

1- Radical treatment

2- Palliative treatment
Options of treatment

- Surgery
- Chemotherapy
- Radiotherapy
- Target therapy
- All of the above
Despite advances in standard therapy, including surgical resection followed by radiation and chemotherapy, the prognosis for patients with Glioblastoma multiforme (GBM) remains poor. Unfortunately, most patients die within 2 years of diagnosis of their disease.
# Summary of reported studies for chemotherapy in GBM

<table>
<thead>
<tr>
<th>References</th>
<th>Regimen</th>
<th>Patients (no.)</th>
<th>Assessable (no.)</th>
<th>CR (%)</th>
<th>PR (%)</th>
<th>SD (%)</th>
<th>PD (%)</th>
<th>Resection² (%)</th>
</tr>
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<tbody>
<tr>
<td><strong>Phase II studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Fetell et al., 1997 [26]</td>
<td>TXL</td>
<td>10</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td>100</td>
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<tr>
<td>Frenay et al., 2000 [27]</td>
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<td>33</td>
<td>33</td>
<td>3</td>
<td>24</td>
<td>51</td>
<td>22</td>
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<td>57</td>
<td>11</td>
<td>28</td>
<td>32</td>
<td>29</td>
<td>50</td>
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<tr>
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<td>50</td>
<td>41</td>
<td>2</td>
<td>25</td>
<td>44</td>
<td>29</td>
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<td>52</td>
<td>42</td>
<td>0</td>
<td>43</td>
<td>53</td>
<td>4</td>
<td>71</td>
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<td>Gruber et al., 1998 [29]</td>
<td>CBDA</td>
<td>25</td>
<td>15</td>
<td>7</td>
<td>46</td>
<td>40</td>
<td>7</td>
<td>40</td>
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<td>Jeremic et al., 1999 [30]</td>
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<td>66</td>
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<td>38</td>
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<td>29</td>
<td>28</td>
<td>0</td>
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<td>41</td>
<td>26</td>
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<td>17</td>
<td>14</td>
<td>0</td>
<td>6</td>
<td>14</td>
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<td>19</td>
<td>19</td>
<td>0</td>
<td>0</td>
<td>53</td>
<td>47</td>
<td>NR</td>
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<td>DFDC+TRS</td>
<td>17</td>
<td>17</td>
<td>0</td>
<td>0</td>
<td>88</td>
<td>12</td>
<td>NR</td>
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<tr>
<td>Grossman et al., 2003 [35]</td>
<td>CDDP+BCNU+Rt</td>
<td>223</td>
<td>219</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NR</td>
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neoadjuvant versus adjuvant (109 neoadjuvant)
## Clinical studies of chemotherapy administration before RTH in GBM

<table>
<thead>
<tr>
<th>Study</th>
<th>Schedule</th>
<th>n</th>
<th>GBM (%)</th>
<th>STRB (%)</th>
<th>OR (%)</th>
<th>PFS (months)</th>
<th>OS (months)</th>
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<tr>
<td>Kirby 1996 [9]</td>
<td>PCV</td>
<td>22</td>
<td>100</td>
<td>NR</td>
<td>5.6</td>
<td>10</td>
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<td>Grossman 1997 [28]</td>
<td>BCNU + CDDP</td>
<td>52</td>
<td>88</td>
<td>29</td>
<td>42</td>
<td>NR</td>
<td>12.9</td>
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<td>Friedman 1998 [10]</td>
<td>Temozolomide</td>
<td>33</td>
<td>100</td>
<td>NR</td>
<td>51</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Frenay 2000 [12]</td>
<td>FOTE + CDDP + VP16</td>
<td>33</td>
<td>100</td>
<td>100</td>
<td>27</td>
<td>NR</td>
<td>10</td>
</tr>
<tr>
<td>Dazzi 2000 [29]</td>
<td>BCNU + CDDP</td>
<td>18</td>
<td>83</td>
<td></td>
<td>54</td>
<td>NR</td>
<td>9</td>
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<tr>
<td>This study</td>
<td>BCNU + temozolomide</td>
<td>40</td>
<td>100</td>
<td>100</td>
<td>42.5</td>
<td>7.4</td>
<td>12.7</td>
</tr>
</tbody>
</table>
Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma for the European Organization for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups and the National Cancer Institute of Canada Clinical Trials Group*

Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma for the European Organization for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups and the National Cancer Institute of Canada Clinical Trials Group* 


Figure 2. Kaplan–Meier Estimates of Progression-free Survival According to Treatment Group.
Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma for the European Organization for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups and the National Cancer Institute of Canada Clinical Trials Group*  
*The entire study period was defined as the period from study entry to seven days after disease progression.

Table 4. Grade 3 or 4 Hematologic Toxic Effects in Patients Treated with Temozolomide.

<table>
<thead>
<tr>
<th>Toxic Effect</th>
<th>Concomitant Temozolomide Therapy (N=284)</th>
<th>Adjuvant Temozolomide Therapy (N=223)</th>
<th>Entire Study Period* (N=284)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>number of patients (percent)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukopenia</td>
<td>7 (2)</td>
<td>11 (5)</td>
<td>20 (7)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>12 (4)</td>
<td>9 (4)</td>
<td>21 (7)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>9 (3)</td>
<td>24 (11)</td>
<td>33 (12)</td>
</tr>
<tr>
<td>Anemia</td>
<td>1 (&lt;1)</td>
<td>2 (1)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Any</td>
<td>19 (7)</td>
<td>32 (14)</td>
<td>46 (16)</td>
</tr>
</tbody>
</table>

Radiation therapy plus concomitant and adjuvant Temozolomide (Temodar®) for newly diagnosed Glioblastoma, when compared with radiation therapy alone, resulted in a 2.5-month increase in median survival and a 16.1% improvement in the 2-year survival rate.
PROLONGED MAINTENANCE TREATMENT WITH TEMOZOLOMIDE AFTER CONCOMITANT RADIO CHEMOTHERAPY IN NEWLY DIAGNOSED GLIOBLASTOMA PATIENTS

E. Franceschi, A. Tosoni, V. Blatt, F. Ruggeri, F. Benevento, S. Bartolini, E. Pozzati, A. Bacci, V. Mazzocchi, A.A. Brandes

Methods: 103 patients were enrolled (mean age 52 [range 20-73] years, total resection or subtotal resection/biopsy were obtained in 102/1 cases).

Conclusion:
In our trial prolonged maintenance TMZ after concurrent RT/TMZ provides promising results. MGMT methylation constitutes a potent prognostic factor and, interestingly, female patients showed an improved overall survival.

TEMZOLOMIDE AND RADIOTHERAPY IN HIGH-GRADEMALIGNANT GLIOMA: UPDATE OF AN OBSERVATIONAL STUDY
R. Ratti1, Z. Coccorullo2, M. Orsatti3, D. Guarneri1, G. Addamo1, G. Colloca1,
A. Venturino1, M. Boccardo4, E. Campora1

**Conclusions:** Even if debulking surgery was feasible in only 74% in this series,
concomitant TMZ and RT followed by 6 courses of TMZ is a safe, feasible
and active regimen in high-grade glioma.

*Annals of Oncology 19 (Supplement 5): v158, 2008*
- Concomitant and adjuvant Temozolomide chemotherapy has been demonstrated to significantly improve median and 2-year survival in a large randomized trial in Glioblastoma [I, A].
- Selecting patients likely to benefit from therapy on the basis of MGMT gene promoter methylation has been suggested [II, B].
- Adjuvant chemotherapy with procarbazine, lomustine and vincristine (PCV regimen) has failed to improve survival in prospective randomized studies [I, A].
- Nevertheless, based on a large meta-analysis [I, A] nitrosourea-based chemotherapy may marginally improve survival in selected patients.
Prognostic Factors

Which patient can benefit from treatment?

Multivariate analysis showed that younger age, surgical treatment and radiotherapy were all dependent prognosis factors for better survival.

Statistically, survival was best for total surgical removal of tumors, followed by tumor gross resection then biopsy.

Clinical status and tumor location were also prognosis factors. The free interval time between total surgery and tumor reappearance was strongly correlated with survival.

This suggests that some grade IV gliomas follow a quicker course, others exhibiting slow growth. Each of the prognosis factors was confirmed in the long-survival patients.

Diagnosis of progressive disease

MR Spectroscopy
A specialized MRI brain that evaluates the chemical composition of a lesion (or lesions) in question.

Indications
Ordered when the etiology (the cause) of a lesion is unclear based on the known information.

Generally used to determine if it is a tumor or not.

MRI is a technique used for the noninvasive detection and anatomical mapping of water protons (hydrogen), whereas MR spectroscopy records protons in intrinsic phosphorus-containing metabolites, sodium, potassium, carbon, nitrogen, and fluorine.
(left), MRI of a Glioblastoma in right parietal region (arrowhead). (right), MR spectroscopy of the lesion shows large lactate-lipid peaks, suggestive of a higher-grade tumor.
Target Therapy

Extracellular
Cell Membrane
Intracellular (cytosol)

Farnesyltransferase inhibitors
- Tipifarnib
- Lonafarnib

Ras-GTP
PLC
Pi3K
PKC
Akt
mTOR

Raf
MEK1,2
MAPK/Erk1,2

HIF1
VEGF

Nucleus

Tyrosine kinase inhibitors
- EGFR: erlotinib, gefitinib, lapatinib AEE788
- PDGFR: imatinib mesylate
- VEGFR: PTK787/ZK222584, AEE788

mTOR inhibitors
- CCI-779
- RAD001
- Rapamycin
- AP23573

Growth Factor Receptor
(e.g., EGFR, PDGFR, IGFR1)

↓ Proliferation
↑ Sensitivity to cytotoxic therapy

↓ Angiogenesis
↑ Apoptosis
Imatinib and hydroxyurea in pretreated progressive glioblastoma multiforme: a patient series

G. Dresemann

Franz-Hospital, Onkologische Abteilung, Düren, Germany

Received 9 March 2005; revised 6 June 2005; accepted 9 June 2005
Figure 3. Survival of 30 progressive glioblastoma multiforme (GBM) patients treated with imatinib and hydroxyurea. (A) Progression-free survival (B) and overall survival.
# Treatment Options for recurrent/progressive GBM

<table>
<thead>
<tr>
<th>Newly diagnosed glioma</th>
<th>Standard</th>
<th>Alternatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glioblastoma</td>
<td>TMZ/RT</td>
<td>Hypofractionated RT for elderly patients or patients with PS scores ≥2</td>
</tr>
<tr>
<td>Anaplastic astrocytoma including oligoastrocytoma</td>
<td>RT</td>
<td>Carmustine/RT → carmustine</td>
</tr>
<tr>
<td>Anaplastic oligodendroglioma</td>
<td>RT</td>
<td>TMZ/RT (→ TMZ)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PCV or TMZ</td>
</tr>
<tr>
<td>Recurrent disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glioblastoma</td>
<td>TMZ\textsuperscript{a}</td>
<td>Depending on prior chemotherapy: Procarbazine, PCV combination regimen</td>
</tr>
<tr>
<td>Anaplastic astrocytoma</td>
<td>TMZ</td>
<td>Irinotecan\textsuperscript{b}</td>
</tr>
<tr>
<td>Anaplastic oligodendroglioma</td>
<td>TMZ or PCV</td>
<td>Erlotinib\textsuperscript{b}</td>
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<td></td>
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<td>Gefitinib\textsuperscript{b}</td>
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<tr>
<td></td>
<td></td>
<td>Imatinib\textsuperscript{b}</td>
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</tbody>
</table>
Conclusion

- Glioblastoma multiforme (GBM) is the most common primary malignant tumor of the central nervous system.
- GBM advances rapidly and tends to recur after treatment, resulting in severe disability and death.
- The 1-year and 2-year relative survival rates for GBM are 29.6% and 9.0%, respectively.
THANKS