Management of Glioblastoma

Timothy Cloughesy, MD
Director, Neuro-Oncology Program
UCLA School of Medicine

Background

• 18,500 new patients diagnosed with primary brain tumors in the United States in 20051,2
  – ~50% gliomas
  – ~50% of all gliomas are glioblastoma multiforme (GBM)
• Among patients with GBM2,3
  – Median survival: 9 to 12 months
  – 2-year survival rates: 8% to 12%

Incidence

Distribution of All Primary Brain and CNS Tumors by Histology

- Glioblastoma: 20.3%
- Astrocytomas: 9.8%
- Ependymomas: 2.3%
- Oligodendrogliomas: 3.7%
- Embryonal, including medulloblastoma: 1.7%
- Meningioma: 30.1%
- Pituitary: 6.3%
- Craniopharyngioma: 0.7%
- Nerve Sheath: 8.0%
- Lymphoma: 3.1%
- Pituitary: 8.3%
- Other: 13.9%

Incidence

Distribution of All Gliomas by Histology Subtypes

- Glioblastoma: 50.7%
- All Other Astrocytomas: 9.1%
- Anaplastic Astrocytoma: 7.9%
- Diffuse Astrocytoma: 1.7%
- Pilocytic Astrocytoma: 5.7%
- Oligodendrogliomas: 9.2%
- Ependymomas: 5.6%
- All Other Gliomas: 10.1%

Risk Factors for Malignant Glioma

• Family history of cancer in 19% of patients1
• Genetically inherited syndromes in 5% of patients with primary brain tumors1
  – Neurofibromatosis types 1 and 2
  – Li-Fraumeni syndrome
  – Von Hippel-Lindau syndrome
  – Turcot syndrome
  – Tuberous sclerosis
• Brain irradiation in childhood2

Gliomagenesis

DCC=deleted in colon cancer; LOH=loss of heterozygosity; RB=retinoblastoma.

Prognostic Classification

- World Health Organization (WHO) Classification System
  - Released in 1993; updated in 2007
  - Tumors classified by cell origin and level of aggression (Grades I–IV)\(^1\,^2\)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Histology</th>
<th>Proportion of All Gliomas</th>
<th>Median Survival (y)(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Pilocytic astrocytoma</td>
<td>&lt;5%</td>
<td>&gt;10</td>
</tr>
<tr>
<td>II</td>
<td>Well-differentiated astrocytoma</td>
<td>20%–30%</td>
<td>5</td>
</tr>
<tr>
<td>III</td>
<td>Anaplastic astrocytoma</td>
<td>20%–30%</td>
<td>3</td>
</tr>
<tr>
<td>IV</td>
<td>Glioblastoma multiforme</td>
<td>40%–50%</td>
<td>1</td>
</tr>
</tbody>
</table>


- Patients with high-grade gliomas identified in the Radiation Therapy Oncology Group (RTOG) database
- Stratification into groups (Class 1–6) based on
  - Age
  - Performance status
  - Histology
  - Neurological function
  - Duration of symptoms
  - Extent of resection
- Prognostic variables may be used to compare trial data

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<th>2-Year Survival (%)</th>
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<td>59</td>
<td>76</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>68</td>
</tr>
<tr>
<td>3</td>
<td>16</td>
<td>35</td>
</tr>
<tr>
<td>4*</td>
<td>11</td>
<td>15</td>
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<tr>
<td>5*</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>6*</td>
<td>4.5</td>
<td>4</td>
</tr>
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\(^{*}\) GBM.


Prognostic Classification

Diagnostic Assessment

- Gold standard\(^1\)
  - Magnetic resonance imaging (MRI) with contrast
  - Computed tomography (CT) scan when MRI is contraindicated
- Adjunctive techniques\(^1,^2\)
  - Magnetic resonance spectroscopy (MRS)
  - Perfusion MRI
  - Positron emission tomography (PET)
- Tissue sample\(^1\)
  - Confirm diagnosis
  - Determine tumor type and grade
  - Molecular genetic analysis


Current Treatment Challenges

- Biologically aggressive tumors
- Brain localization
- Pharmacologic delivery
  - Blood-brain barrier
- Limited therapeutic response
  - Intrinsic resistance to conventional therapies
- Microenvironment (hypoxia, interstitial pressure, angiogenesis)
- Neurotoxicity of glioma-directed treatments
  - Susceptibility of normal brain to therapy-related injury
- Spread of malignant cells into brain parenchyma


Current Treatment: Surgery

- Rationale for extensive resection
  - Provides adequate tissue for diagnosis
  - Palliates mass effect
  - Allows for improvements in tumor-related signs and symptoms
  - May increase survival
  - Helps halt disease progression by eliminating resistance clones

Current Treatment: Surgery

• Challenges
  – Biopsy vs resection
  • Tumor location
  • Patient factors
  – Co-administration of local therapy
  • Treatment toxicity
  • Clinical trial exclusion

Current Treatment: Surgery

Maximal Safe Resection

• Challenges
  – Biopsy vs resection
  • Tumor location
  • Patient factors

Current Treatment: Surgery

Extent of Tumor Resection Is Associated With Improved Outcomes

<table>
<thead>
<tr>
<th>Study</th>
<th>Conclusion</th>
</tr>
</thead>
</table>

Current Treatment: Surgery Plus Local Therapy

• Carmustine (BCNU) wafers
  – Polyanhydride wafers, 7.7 mg carmustine (BCNU)1
  – Polyanhydride wafers, 7.7 mg carmustine (BCNU)1
  – Approval
    • 1996 for recurrent GBM as adjunct to surgery2
    • 2003 expanded for all high-grade gliomas, including newly diagnosed3
  – Local delivery obviates the blood–brain barrier
  – Lower toxicity than systemic chemotherapy


Current Treatment: Surgery Plus Local Therapy

– Positive persistent drug infusion using intracranial catheters developed by National Institutes of Health in 1990s1
  – Convection-enhanced delivery (CED)1
  – Circumvents blood–brain barrier, limits systemic toxicity
  – Extends challenges in determining efficacy2

Current Treatment: Radiation Therapy (RT)

- Challenges
  - Recurrence is the major source of therapeutic failure
  - Surgery and radiation therapy often fail to prevent recurrence
  - Most recurrent gliomas occur at close proximity to initial tumor

<table>
<thead>
<tr>
<th>Distance from Edge of Initial Tumor (cm)</th>
<th>Incidence (% of All Recurrent Gliomas)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>60</td>
</tr>
<tr>
<td>1–2</td>
<td>19</td>
</tr>
<tr>
<td>2–3</td>
<td>18</td>
</tr>
<tr>
<td>&gt;3</td>
<td>3</td>
</tr>
</tbody>
</table>


- RTOG Trial Analyses
  - Improved outcomes with involved-field vs. whole-brain RT
  - Dose-response relationship: best response with 60 to 65 Gy conventional external beam RT (cEBRT)
  - No apparent survival benefit with:
    - >65 Gy cEBRT
    - Conformal RT
    - Accelerated or hyperfractionated schedules
    - Boost gamma knife RT
    - Brachytherapy boost


Current Treatment: Chemotherapy

- Challenges
  - Issues of efficacy
  - Intrinsic resistance
  - Pharmacologic (tumor delivery)
  - Concurrent medications
    - Anticonvulsants
    - Steroids
  - Systemic toxicity
  - Response measurements

Three Major Meta-Analyses

<table>
<thead>
<tr>
<th></th>
<th>Fine et al.1</th>
<th>Stewart 2</th>
<th>Spiegel et al.3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date of meta-analysis</td>
<td>1993</td>
<td>2002</td>
<td>2007</td>
</tr>
<tr>
<td>Trials analyzed, n</td>
<td>16</td>
<td>12</td>
<td>16</td>
</tr>
<tr>
<td>Patients analyzed, n</td>
<td>&gt;3,000</td>
<td>3,004</td>
<td>&gt;3,000</td>
</tr>
<tr>
<td>Agent(s) used</td>
<td>Various</td>
<td>Various</td>
<td>Various</td>
</tr>
<tr>
<td>Absolute increase in survival, %</td>
<td>10.1</td>
<td>6.0</td>
<td>15.9*</td>
</tr>
<tr>
<td>1 year</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 year</td>
<td>8.6</td>
<td>4.0</td>
<td>17.0*</td>
</tr>
</tbody>
</table>

* TMZ treatment group only.


Current Treatment: Temozolomide (TMZ)

- Methylating agent
  - Cytotoxic product is O6-methylguanine DNA adducts
  - Initiates mismatch repair pathway recycling, resulting in apoptotic cell death

- Efficacy
  - Activity in newly diagnosed anaplastic glioma
  - Activity in recurrent anaplastic astrocytoma
  - Activity in recurrent GBM
  - Activity in adjuvant treatment of GBM1,5

Current Treatment: Temozolomide
European Organization for the Research and Treatment of Cancer (EORTC)/National Cancer Institute of Canada (NCIC) Treatment Platform

Radiotherapy (RT): Focal, 60 Gy in 6 wk to tumor volume plus 2- to 3-cm margin

TMZ:
- During RT: 75 mg/m²/d (including weekends) for up to 49 d; administered 1–2 h before RT or on days without RT

Maintenance: 150–200 mg/m²/d × 5 d, for up to 6 cycles; antiemetic prophylaxis

PCP = Pneumocystis carinii pneumonia.


### EORTC/NCIC Trial

- **Primary endpoint:** overall survival
- **Secondary endpoints:** progression-free survival, quality of life (QOL), safety
- **No negative impact on QOL**

- **5-year follow-up data:** A benefit of combined therapy was recorded in all subgroups

<table>
<thead>
<tr>
<th>Survival</th>
<th>RT</th>
<th>RT + TMZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-year</td>
<td>10.4%</td>
<td>26.5%</td>
</tr>
<tr>
<td>3-year</td>
<td>10.9%</td>
<td>27.3%</td>
</tr>
<tr>
<td>4-year</td>
<td>4.4%</td>
<td>16.0%</td>
</tr>
<tr>
<td>5-year</td>
<td>3.0%</td>
<td>12.1%</td>
</tr>
</tbody>
</table>


### DNA repair

- **O-6-methylguanine-DNA-methyltransferase (MGMT)**
- Also known as hepatic O-6-alkylguanine-DNA alkyltransferase (AGT, AGAT)
- Reverses alkylation at O-6 position of guanine, prevents cell death
- High tumor levels cause resistance to alkylating agents
- Low tumor levels cause susceptibility to alkylating drugs

- **MGMT and TMZ**
- Retrograde analysis of MGMT tumor content and TMZ sensitivity in EORTC/NCIC trial data
- Low levels of MGMT in glioblastoma tumors correspond with improved response to TMZ


### MGMT Promoter Methylation and GBM: Outcomes

<table>
<thead>
<tr>
<th>MGMT</th>
<th>TMZ</th>
<th>RT only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>2-yr</td>
<td>3-yr</td>
</tr>
<tr>
<td>Unmethylated TMZ</td>
<td>12.6 mns</td>
<td>14.8%</td>
</tr>
<tr>
<td>Methylated TMZ</td>
<td>11.8 mns</td>
<td>1.8%</td>
</tr>
<tr>
<td>RT only</td>
<td>15.3 mns</td>
<td>23.9%</td>
</tr>
</tbody>
</table>


### Current Treatment: Temozolomide

**Post-Radiation TMZ Dosing Regimens**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Dose and Schedule</th>
<th>Drug Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard monthly (5/28)</td>
<td>150–200 mg/m² × 5 d q28d</td>
<td>1</td>
</tr>
<tr>
<td>Continuous daily*</td>
<td>50 mg/m²</td>
<td>–</td>
</tr>
<tr>
<td>Continuous (21/28)</td>
<td>75 mg/m²/d × 7 days for 4 wk</td>
<td>2.1</td>
</tr>
<tr>
<td>Alternating (21/28)</td>
<td>65–100 mg/m²/d × 21d q28d</td>
<td>2.8</td>
</tr>
<tr>
<td>Alternating weekly (7/14)</td>
<td>135–150 mg/m² × 7–10 qd</td>
<td>3.2</td>
</tr>
<tr>
<td>Twice daily*</td>
<td>250 mg/m² × 8 doses</td>
<td>–</td>
</tr>
<tr>
<td>90–100 mg/m² × 9 doses</td>
<td>–</td>
<td></td>
</tr>
</tbody>
</table>


*Approved by the FDA.

### Current Treatment: Temozolomide

**RTOG 0525**
- Completed Phase III trial comparing conventional adjuvant TMZ with dose-intensive TMZ in newly diagnosed GBM
- *n=1154*

1. To 12 cycles may be given if continued improvement shown by MRI scan, decreasing corticosteroid requirement, improvement in performance status, or improvement in neurological function.
Current Treatment: Temozolomide

Remaining Questions

• Which aspect of the EORTC regimen has influenced survival?
• Which new treatments can be added to the EORTC regimen?
• How much TMZ should be given following radiation therapy (dose and duration)?
• Pseudoprogression?
  – May appear as progression either clinically or by imaging
  – May result in erroneous treatment modification
  – Consider continuation of treatment despite early progressive changes

Pseudoprogression

Pre-op

Post-op

Post-XRT/TMZ

After 2 cycles TMZ

After 4 cycles TMZ

Best Initial Treatment Strategies: Summary

• Maximum safe resection
• Conventional fractionated EBRT (as defined by RTOG and EORTC studies)
• RT and concomitant TMZ (EORTC/NCIC study)
• Post-RT TMZ chemotherapy for 6 months (EORTC/NCIC study)

Upcoming Clinical Trial: Temozolomide + Bevacizumab

RTOG 0825

• Double-blind, placebo-controlled, phase III trial combining temozolomide and bevacizumab
• Anticipated to start in early 2009

Standard Arm

Chemoradiation + temozolomide + PLACIEBO

Experimental Arm

Chemoradiation + temozolomide + BEVACIZUMAB


Options for Salvage Therapy

• Re-operation (if possible and clinically appropriate)
• Re-irradiation (if no other options or small-volume recurrence)
• Local therapy (in conjunction with re-operation or investigational therapy)
• Chemotherapy
• Targeted therapy (i.e., bevacizumab)
• Investigational therapy
Time Course of Pseudo-Progression (PP)

Keywords: pseudoprogression, Tim, time course

GenenUser, 3/30/2009
**Treatment Strategies: Salvage**

- Re-operation and regional drug administration
  - BCNU wafers
  - Approved by Food and Drug Administration as salvage therapy
- Controversial strategies (less compelling evidence)
  - Stereotactic re-irradiation
  - Balloon catheter and radioactive iodine (GliaSite Radiation Therapy System)

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**Recurrent Glioma: Historical Controls**

<table>
<thead>
<tr>
<th>Author</th>
<th>Histology Treatment</th>
<th>Number</th>
<th>6-Month PFS</th>
<th>Median Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wong J Clin Oncol 1999</td>
<td>No prior TMZ</td>
<td>225</td>
<td>15%</td>
<td>25 weeks</td>
</tr>
<tr>
<td></td>
<td>GBM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No prior TMZ AA</td>
<td>150</td>
<td>31%</td>
<td>47 weeks</td>
</tr>
<tr>
<td>Lamborn Neuro Oncol 2008</td>
<td>No prior TMZ</td>
<td>146</td>
<td>28%</td>
<td>40 weeks</td>
</tr>
<tr>
<td></td>
<td>Prior TMZ</td>
<td>231</td>
<td>9%</td>
<td>26 weeks</td>
</tr>
</tbody>
</table>

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**What Are the Targets?**

- Genetic abnormalities or pathways activated as a consequence of genetic abnormalities
  - RTK/MAPK/PI3K
  - P53
  - RB1
  - Or critical messengers of those pathways
- End biologic processes
  - Invasion
  - Angiogenesis
  - Cell survival
  - Cell metabolism
- Unique cell populations
  - Stem cells
  - Endothelial cell
- Immune therapies

---

**Results of Targeted Therapy**

- RTK (imatinib, gefitinib, erlotinib, AEE788, dasatinib, XL184)
- FTI (tipifarnib)
- Avb3 integrins (cilengitide)
- Multikinase (sorafenib, sunitinib)
- SRC (dasatinib)
- mTor (temsirolimus, sirolimus, everolimus)
- PI3K (XL765, BEZ235)
- PKC (enzastaurine, tamoxifen)
- VEGFR (PTK, AEE788, pazopanib, bevacizumab, AZD2171, aflibercept, CT-322)
- Temozolomide
6-Month PFS and OS: Historical Data

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>6-mo PFS 6, % (95% CI)</strong></td>
<td>TMZ: 28 (21-36) Other: 9 (6-13) Total: 16 (12-20)</td>
<td>GBM: 15 (10-19) AA: 31 (24-39) Total: 21 (17-26)</td>
</tr>
<tr>
<td><strong>Median survival, wks (95% CI)</strong></td>
<td>TMZ: 40 (33-47) Other: 26 (23-29) Total: 30 (27-33)</td>
<td>GBM: 25 (23-28) AA: 47 (38-64) Total: 30</td>
</tr>
</tbody>
</table>

[^1]: Patients from NABTC phase II studies between February 1998 - December 2002.
[^2]: Patients from 8 phase II studies with 225 recurrent GBM and 150 recurrent AA.


What Are the Targets?
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  - Cell survival
  - Cell metabolism
- Unique cell populations
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  - Endothelial cell
- Immune therapies

Inhibiting VEGF

Bevacizumab
- Humanized antibody against VEGF-A
  - At least 7 isoforms of VEGF
  - Half-life, 20 days
- VEGF receptors are Flt-1 (VEGFR-1) and Flk-1/KDR (VEGFR-2)
Figure 1. Kaplan-Meier survival curves for all patients. A) Progression-free survival and B) Overall survival of bevacizumab-treated versus control group.

Figure 2. Kaplan-Meier survival curves by age. A) Progression-free survival for patients age <55, B) Progression-free survival for patients age >55, C) Overall survival for patients age <55, and D) Overall survival for patients age >55.

Figure 3. VEGF expression by age via DNA microarray analysis.
**BV Improves PFS But not OS**

**Prognostic Classification**

**RTOG Recursive Partitioning Classification System**

- Patients with high-grade gliomas identified in the Radiation Therapy Oncology Group (RTOG) database
- Stratification into groups (Class 1–6) based on:
  - Age
  - Performance status
  - Histology
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</tr>
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<td>5*</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>6*</td>
<td>4.5</td>
<td>4</td>
</tr>
</tbody>
</table>

*GBM.


**RPA Class III/IV Does Not Benefit from BV for PFS or OS**

**RPA Class V/VI Benefits from BV for PFS and OS**

**Considerations for Challenging Patient Groups**

- Elderly
  - Survival rates
  - EORTC/NCIC regimen may be used in otherwise healthy elderly
  - Accelerated hypofractionated radiotherapy (40 Gy in 15 fractions)
  - Primary chemotherapy (SBGT TMZ dosing schedule)
  - Radiotherapy vs. supportive care showed benefit
  - Bevacizumab and Temozolomide (UCLA/Kaiser)

<table>
<thead>
<tr>
<th>Age</th>
<th>1 Year</th>
<th>2 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥65 years</td>
<td>16.8%</td>
<td>2.7%</td>
</tr>
<tr>
<td>≥75 years</td>
<td>8.1%</td>
<td>1.4%</td>
</tr>
</tbody>
</table>

Frequent Genetic Alterations in Three Critical Signaling Pathways

Thank You