Neuro-Oncology

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DISCLOSURES

Off-Label Usage
  • Rituximab (Genentech)

Interests
  • None
Problems Unique to CNS Tumors

- ≈ 100 different tumor types
- Drug delivery
  - Blood-brain barrier
  - Difficult/complicated pharmacology
    - Multiple compartments (blood, brain parenchyma, CSF)
    - Drug-drug interactions
- CNS is a relative immunological sanctuary
- Highly infiltrative nature and potential CSF spread of primary brain tumors
- Exquisite sensitivity to and absolute requirement for the host target organ
WHO Classification of CNS Tumors 2007

1. Tumors of Neuroepithelial Tissue
2. Lymphomas
3. Tumors of the Meninges
4. Tumors of Cranial and Paraspinal Nerves
5. Germ Cell Tumors
6. Tumors of the Sellar Region
7. Metastatic Tumors
Distribution of Primary Brain and CNS Tumors by Histology (N = 311,202).

Gliomas (ICD-O-3: 9380-9384, 9391-9460, 9480) account for 29% of all tumors and 80% of malignant tumors.

Dolecek T A et al. Neuro Oncol 2012;14:v1-v49
Tumors of Neuroepithelial Tissue

1. Astrocytic tumors
2. Oligodendroglial tumors
3. Oligoastrocytic tumors
4. Ependymal tumors
5. Choroid plexus tumors
6. Other neuroepithelial tumors
7. Neuronal and mixed neuronal-glial tumors
8. Pineal parenchymal tumors
9. Embryonal tumors

GLIOMAS
Distribution of Primary Brain and CNS Gliomas by Histology Subtypes (N = 90,828)

Glioma malignant, NOS 7.2%
Ependymal tumors 6.7%
Oligodendroglioma 6.2%
Pilocytic astrocytoma 5.1%
Diffuse astrocytoma 9.5%
Anaplastic astrocytoma 5.9%
Oligoastrocytic tumors 3.3%
All Other Glioma 1.9%
Glioblastoma 54.0%
Astrocytomas and glioblastomas account for 76% of all gliomas

† ICD-O-3 codes = 9380-9384,9391-9460,9480

Dolecek T A et al. Neuro Oncol 2012;14:v1-v49

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Dysregulated pathways in gliomas

**Cell-of-Origin: Differentiated Glial or Stem or Progenitor Cells**

- **Low-Grade Astrocytoma (5–10 yr)*** (WHO Grade II)
  - LOH 19q (~50%)
  - RB mutated (~25%)
  - CDK4 amplified (15%)
  - MDM2 overexpressed (10%)
  - P16Ink4a/P14ARF loss (4%)
  - LOH 11p (~30%)

- **Anaplastic Astrocytoma (2–3 yr)** (WHO Grade III)
  - LOH 10q (~70%)
  - DCC loss (~50%)
  - PDGFR-α amplified (~10%)
  - PTEN mutated (~10%)
  - PI3K mutated/amplified (~10%)
  - VEGF overexpressed

- **Secondary Glioblastoma (12–15 mo)** (WHO Grade IV)
  - VEGF overexpressed

- **Primary Glioblastoma (12–15 mo)** (WHO Grade IV)
  - VEGF overexpressed

- **Low-Grade Oligodendroglioma (5–10 yr)*** (WHO Grade II)
  - P16Ink4a/P14ARF loss
  - RB mutated (~65%)
  - p53 mutated
  - PTEN loss
  - LOH 9p, 10q
  - CDK4/EGFR/MYC amplified
  - VEGF overexpressed

- **Anaplastic Oligodendroglioma (3–5 yr)*** (WHO Grade III)

Wen PY, NEJM 2008
Gliomas: Staging & Classification

- TNM classification not relevant
- Spread outside CNS exceedingly rare
- Histology and grade determined by cellular characteristics

<table>
<thead>
<tr>
<th>WHO Classification</th>
<th>Histologic Subtype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I</td>
<td>Pilocytic astrocytoma</td>
</tr>
<tr>
<td>Grade II</td>
<td>Astrocytoma</td>
</tr>
<tr>
<td></td>
<td>Oligodendroglioma</td>
</tr>
<tr>
<td></td>
<td>Mixed glioma</td>
</tr>
<tr>
<td>Grade III</td>
<td>Anaplastic astrocytoma</td>
</tr>
<tr>
<td></td>
<td>Anaplastic oligo</td>
</tr>
<tr>
<td></td>
<td>Mixed anaplastic glioma</td>
</tr>
<tr>
<td>Grade IV</td>
<td>Glioblastoma</td>
</tr>
</tbody>
</table>
Diffusely Infiltrating Astrocytomas
Malignancy Criteria

- A  Atypia
- M  Mitoses
- E  Endothelial Proliferation
- N  Necrosis
## Importance of Glioma Grading

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Median Survival (yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-grade oligodendroglioma</td>
<td>10-12</td>
</tr>
<tr>
<td>Low-grade astrocytoma</td>
<td>5-6</td>
</tr>
<tr>
<td>Anaplastic oligodendroglioma</td>
<td>5+</td>
</tr>
<tr>
<td>Anaplastic astrocytoma</td>
<td>3</td>
</tr>
<tr>
<td>Glioblastoma</td>
<td>1</td>
</tr>
</tbody>
</table>
Glioblastoma
Atypia + Mitoses

Endothelial Proliferation
Palisading Necrosis
Frequent genetic alterations in three critical signalling pathways.

Two Molecular Pathways to Glioblastoma

Cells of origin?????

- EGFR amplification/mutation (7p12)
- p16 loss (9q26)
- LOH 10
- PTEN mutation (10q24)
- RB alterations (13q13)

Astrocytoma

- IDH1 mutation
- PDGF, FGF2 over-expression
- p53 mutation
- CDK4 amplification (12q13)
- RB loss
- LOH 19q
- LOH 10q
- PTEN mutation

Anaplastic Astrocytoma

Primary GBM

Secondary GBM

Cells of origin??????
Glioblastoma - Management

• Surgery
  – Bx or resection required for diagnosis
  – Resection improves OS by average 2-4 mo
  – “Maximal safe resection”
    • Mapping
    • Awake craniotomy
    • Intraoperative MRI

• Radiation
  – Fractionated RT improves OS (60 Gy/30 fx)
  – In frail/elderly, 40 Gy/15 fractions reasonable
  – No proven role for radiosurgery
RTOG 9305: Phase III Trial of Radiosurgical Boost for GBM

![Graph showing survival rates over months with median survival times for RT and SRS+RT treatments.]

- RT: Median Survival Time = 13.6 months, n = 97
- SRS+RT: Median Survival Time = 13.5 months, n = 89

Survival rate vs. Months

Median Survival Time

RT: 13.6 months
SRS+RT: 13.5 months

P = 0.57
Meta-analysis of Chemotherapy in High-Grade Glioma: The Old Days

Chemotherapy yields a small survival benefit

Survival

Time since randomization, years

Patients at Risk

RT-CTX

RT

Events

Total

RT-CTX

RT

1698

1306

1484

1175

1698

1306

N=3004

Lancet. 2002;359:1011-1018
The “Stupp” Trial: Treatment Schema

Concurrent TMZ/RT

Adjuvant TMZ

Weeks 6 10 14 18 22 26 30

RT Alone

Temozolomide 75 mg/m² po qd for 6 weeks, then 150–200 mg/m² po qd d1–5 every 28 days for 6 cycles

Focal RT daily — 30 x 200 cGy
Total dose 60 Gy
Progression-Free Survival

<table>
<thead>
<tr>
<th></th>
<th>RT</th>
<th>TMZ/RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, mo</td>
<td>5.0</td>
<td>6.9</td>
</tr>
<tr>
<td>1-yr PFS</td>
<td>9%</td>
<td>27%</td>
</tr>
<tr>
<td>2-yr PFS</td>
<td>2%</td>
<td>11%</td>
</tr>
<tr>
<td>HR [95% C.I.]</td>
<td>0.54</td>
<td>[0.45-0.64]</td>
</tr>
<tr>
<td>p</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

Overall Survival

- Median OS, mo:
  - RT: 12.1
  - TMZ/RT: 14.6
- 2-yr survival:
  - RT: 10%
  - TMZ/RT: 27%
- HR [95% C.I.]:
  - RT: 0.63 [0.52-0.75]
  - TMZ/RT: \( p < 0.0001 \)

TMZ – longer term f/u
Stupp Trial: Companion Molecular Analysis

- Small studies suggested epigenetic silencing of *MGMT* via promoter hypermethylation portended good outcome
- 45% of pts had promoter hypermethylation

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median Survival (mo)</th>
<th>2-yr survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT/TMZ Methylated</td>
<td>22</td>
<td>46</td>
</tr>
<tr>
<td>RT Methylated</td>
<td>15</td>
<td>23</td>
</tr>
<tr>
<td>RT/TMZ Unmethylated</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>RT Unmethylated</td>
<td>12</td>
<td>&lt; 2</td>
</tr>
</tbody>
</table>

Bevacizumab Alone and in Combination With Irinotecan in Recurrent Glioblastoma

Henry S. Friedman, Michael D. Prados, Patrick Y. Wen, Tom Mikkelsen, David Schiff, Lauren E. Abrey, W.K. Alfred Yung, Nina Paleologos, Martin K. Nicholas, Randy Jensen, James Vredenburgh, Jane Huang, Maxxia Zheng, and Timothy Cloughesy

Phase II Trial of Single-Agent Bevacizumab Followed by Bevacizumab Plus Irinotecan at Tumor Progression in Recurrent Glioblastoma

Teri N. Kreisl, Lyndon Kim, Kraig Moore, Paul Duic, Cheryl Royce, Irene Stroud, Nancy Garren, Megan Mackey, John A. Banman, Kevin Camphausen, John Park, Paul S. Albert, and Howard A. Fine
“BRAIN” Study Design

Patients with GBM Randomized by 1st or 2nd Relapse (N=167)  
1:1  

Bevacizumab* (n=85)  

Bevacizumab /CPT11** (n=82)  

Optional Post-PD Phase  
Bevacizumab + CPT-11  

1st Progressive Disease (PD)  

Stratification by:  
• KPS: 70-80, 90-100  
• 1st, 2nd relapse
# Efficacy

<table>
<thead>
<tr>
<th></th>
<th>BV Alone (n=85)</th>
<th>BV+CPT-11 (n=82)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PFS6, %</strong></td>
<td>42.6</td>
<td>50.3</td>
</tr>
<tr>
<td><strong>ORR, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>1.2</td>
<td>2.4</td>
</tr>
<tr>
<td>PR</td>
<td>27.1</td>
<td>35.4</td>
</tr>
<tr>
<td><strong>Median Duration of Response (months)</strong></td>
<td>5.6</td>
<td>4.3</td>
</tr>
</tbody>
</table>
Bevacizumab: Conclusions

- Bevacizumab active agent in recurrent GBM
  - Alone and in combination with CPT-11
  - Responding patients had stable or decreasing corticosteroid use
- Bevacizumab is well tolerated
  - Low rates of bleeding, wound dehiscence
- No clear benefit from CPT-11
- Single-agent bevacizumab received FDA accelerated approval in 5/09
Bevacizumab in Newly Diagnosed GBM

Primary End Points, According to Study Group.

**RTOG 0825**

**AVAglio**

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*The NEW ENGLAND JOURNAL of MEDICINE*
Lower-Grade (II & III) Gliomas
Development and progression of astrocytic and oligodendroglial tumors

Cell of Origin

- IDH mutation (80+%)  
- BRAF fusion/mutation  
- p53 pathway mutation (50%)  
- t(1;19) (40%)

- Astrocytoma
- Mixed glioma
- Oligodendroglioma

Pilocytic astrocytoma +
Anaplastic (Grade III) Gliomas

Oligo

Astrocytoma
Anaplastic Glioma Imaging

- T2 bright, enhancement variable
Anaplastic Glioma: Importance of 1p/19q Status

• Prognostic

• Predictive

Treatment of Anaplastic Gliomas

- **Anaplastic Astrocytoma**
  - Maximal safe resection
  - Fractionated RT (60 Gy)
  - Adjuvant chemo?
    - Soft old data for PCV
    - ? benefit w/IDH mutation
    - RT/TMZ under study (CATNON)
    - TMZ, PCV or BCNU for salvage
  - Median OS ≤ 3 yrs

- **Anaplastic Oligo**
  - Maximal safe resection
  - RT (60 Gy)
  - Adjuvant chemo
    - PCV proven benefit if 1p/19q codeletion
    - Before or after RT
    - RT/TMZ under study (CODEL trial)
  - Chemo alone to defer RT under study
  - Median OS 7-15 yrs
Low-Grade (II) Gliomas
LGG Under the Microscope

Astrocytoma

Oligodendrogliaoma
Low-Grade Glioma Clinical Features

- Younger patients (median 35)
- Typical presentation seizures or incidental
- T2/FLAIR-hyperintense w/o sig enhancement
LGG: Management

- When to intervene
  - Initial observation an option in young pts (< 40)
- First step: debulking versus biopsy
  - Maximal safe resection
    - For some, this means biopsy only
    - Near-total resection + younger pt or favorable molecular → subsequent observation an option

Houiller C, Neurology 2010
LGG: Standard of Care Evolving?

- Fractionated RT to tumor/margin
  - Historical SOC
  - No dose responsiveness between 45 and 64Gy
    - Usual dose 50-54Gy in 1.8Gy fractions
  - Partial responses in ≈ 30%
  - Delays TTP by median 2 yrs
    - No OS benefit from early RT c/w observation → RT
  - Debate about cognitive impact
    - Common attention/memory ↓ in long-term survivors
Chemotherapy to Defer RT?

- Several temozolomide studies suggest median TTP with chemo alone $\approx 3$ yrs
- Phase III TMZ vs RT (EORTC-NCIC, ASCO 2013)
  - 477 pts randomized, median f/u 45 mo
  - PFS: RT 47 vs TMZ 40 mo (NS)
    - 58 vs 55 for 1p-deleted, 41 vs 30 if 1p-intact ($p = .06$)
  - OS data not mature
Chemoradiation for LGG?

- RTOG 9802: Ph III RT vs RT → PCV x 6
  - Initially +ve for PFS but negative for OS (JCO 2012)
  - Longer f/u: Positive for OS (ASCO 2014)
    - OS 13.3 vs 7.8 years
    - No molecular analysis to date

- RT/TMZ
  - Ph II single arm (RTOG 0424): well-tolerated and OS-3 better than historical controls
  - Ph III trial ECOG E3F05 stopped 2° 9802 results
Primary CNS Lymphoma
Background and Epidemiology

- Almost always diffuse large B-cell
- Two diseases
  - Immunosuppressed patients
  - Immunocompetent patients
- Median age 60
- No systemic disease, but assn w/ocular lymphoma
Typical Imaging
Initial Diagnosis

- Biopsy – no need to debulk
- Staging
  - Ocular exam, CSF occ yield diagnosis
  - CT C/A/P vs body PET-CT
  - HIV test
  - Testicular US?
- Steroids
  - Lyse lymphoma cells and occasionally render biopsy non-diagnostic
  - Very useful in treating symptoms and improving MRI
Radiation: Proven Benefits

- 50% CR rate but OS only 12 mo
- Whole brain disease → WBRT
- No apparent benefit to craniospinal RT
- Problem: Severe cognitive SEs in elderly
  - NPH-like picture
Neo-Adjuvant Chemotherapy

- High-dose methotrexate most active agent
  - Forms backbone of several regimens
  - Lipid-soluble alkylators often added (TMZ, PCBZ)
  - Rituximab – poor CSF penetration (< 2%) but has single-agent activity, .: role uncertain

- Post-MTX ara-C appears to improve OS
- Median OS ≈ 3 years
- CR rates up to 70%
  - Spawned interest in deferring RT

Ferreri, Lancet 2009
Radiation-Deferring Strategies

- G-PCNSL-SG-1: Phase III study of chemo ± post-chemo WBRT consolidation
  - WBRT improved PFS but not OS
  - Ambitious but flawed study
- In CR pts > 60 (and sometimes younger), many experts defer WBRT
- Lower-dose consolidation WBRT under study
- Ongoing studies of high-dose chemo consolidation in CR pts in lieu of WBRT