What’s New in Neuro-Oncology: Updates from Recent ASCO Meetings

Sponsored by the University of Chicago Brain Tumor Center & the Heinrich Kluver Memorial Lectureship Endowment
Welcome and Introduction

Infiltrating gliomas remain the most common and, therefore, vexing, clinical problem in neuro-oncology. Significant advances in patient outcomes have been slow, despite substantial investments of creative thinking, time, energy, and financial resources. Our goals are: 1) to review recent clinical trial results and 2) to discuss their impact on future directions and challenges in providing optimal care.
PROBLEMS UNIQUE TO NEURO-ONCOLOGY

• Small changes in tumor size and location can have significant impact on functional status.

• Brain anatomy and physiology limit therapeutic options.
  – Surgery
  – Radiotherapy
  – chemotherapy
PROGRAM

• Bevacizumab in Glioblastoma
  • M. Kelly Nicholas, MD, PhD

• Anaplastic Gliomas
  • Rimas Lukas, MD

• Combining Chemotherapy and Radiotherapy in Low Grade Gliomas
  • Steve Chmura, MD, PhD

DISCUSSION
Updates in the Radiotherapeutic Management of Low-grade Gliomas

Steven J. Chmura, MD PhD
Department of Radiation and Cellular Biology
University of Chicago Medical Center
October 15, 2013
Introduction to Low-grade Gliomas

- Low-grade gliomas (LGG) = 20-30% of gliomas

- 70-80% of patients present with new-onset seizures

- Umbrella term for various histologies
  - Astrocytomas (67%)
  - Oligodendroglioma (13%)
  - Oligoastrocytoma (19%)

- Maximal safe surgical resection continues to be the diagnostic and therapeutic intervention of choice
Radiotherapy in LGG: Key Questions

• Do all patients benefit from immediate RT or can some patients be observed?
  – Timing of RT
  – EORTC 22845 (“Non-believers trial”)

• Predominant Pattern of failure is in RT field
  – Is there a role of dose escalation?
  – EORTC 22844 (“Believers trial”)
  – Intergroup/NCCTG/RTOG/ECOG
EORTC 22845 – “Non-believers Trial”

- **Goal:** To assess the efficacy of immediate radiation therapy compared to deferring until progression

Eligibility:
- Supratentorial LGG
- 16-65 years old
- KPS ≥50

Randomized:
- Observation until time of recurrence
  - N=157

Early RT (54 Gy/1.8 Gy per fraction by week 8)
- N=154

Van Den Bent, Lancet, 2005
EORTC 22845: Results

5 year PFS: 55% vs 35%

Van Den Bent, Lancet, 2005
EORTC 22845: Results

<table>
<thead>
<tr>
<th></th>
<th>Early RT</th>
<th>Delayed RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS</td>
<td>5.3 years</td>
<td>3.4 years (p&lt;0.01)</td>
</tr>
<tr>
<td>Median survival</td>
<td>7.4 years</td>
<td>7.2 years</td>
</tr>
<tr>
<td>5-year overall survival</td>
<td>≈68%</td>
<td>≈66%</td>
</tr>
<tr>
<td>1 year seizures</td>
<td>25%</td>
<td>41% (p=0.03)</td>
</tr>
</tbody>
</table>

Conclusions:
- Early RT is associated with improved PFS but not OS
- Early RT results in better seizure control
EORTC 22844 – “Believers trial”

• Goal: To identify the role of dose escalation in LGG

Eligibility
Supratentorial LGG
16-65 years old
Neurologic Deficit ≤3
KPS ≥60

Randomized

45 Gy/1.8 Gy per fraction
N=171

59.4 Gy/1.8 Gy per fraction
N=172

Karim, IJROBP, 1996
## EORTC 22844: Results

<table>
<thead>
<tr>
<th></th>
<th>45 Gy</th>
<th>59.4 Gy</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-year OS</td>
<td>&lt;60%</td>
<td>&lt;60%</td>
</tr>
<tr>
<td>5-year CSS</td>
<td>48%</td>
<td>44%</td>
</tr>
<tr>
<td>5-year PFS</td>
<td>47%</td>
<td>50%</td>
</tr>
</tbody>
</table>

**Conclusions:**
- No benefit to dose escalation
EORTC Prognostic Factors

• Pooled analysis of EORTC 22844 and 22845

Poor Prognostic Factors

• Age $\geq$40
• Astrocytoma histologic subtype
• Largest diameter $\geq$6 cm
• Tumor crossing midline
• Neurologic deficits before surgery

Pignatti, J Clin Oncol, 2002
Prognostic Factors for Survival in Adult Patients With Cerebral Low-Grade Glioma

By Francesco Pignatti, Martin van den Bent, Desmond Curran, Channa Debruyne, Richard Sylvester, Patrick Therasse, Denes Áfra, Philippe Cornu, Michel Bolla, Charles Vecht, and Abul B.M.F. Karim for the European Organization for Research and Treatment of Cancer Brain Tumor Cooperative Group and Radiotherapy Cooperative Group

Fig 3. Neurologic deficit (construction set).

Fig 5. Tumor crossing the midline (construction set).
A Phase II Study of a Temozolomide-Based Chemoradiotherapy Regimen for High Risk Low-Grade Gliomas: Preliminary Results of RTOG 0424

- Barbara Jean Fisher, Jeff Lui, David R. Macdonald, Glenn Jay Lesser, Stephen Coons, David Brachman, Samuel Ryu, Maria Werner-Wasik, Jean-Paul Bahary, Chen Hu, Minesh P. Mehta

ASCO 2013
J Clin Oncol 31, 2013 (suppl; abstr 2008)
Design

• Single Arm Phase II (first developed RND)

• Compare to 3y PFS/OS historical controls from EORTC pooled analysis

• **3-5 risk factors = high risk**

• Statistics
  – One Sided Design
  – Detect 43% increase mOS 40.5 to 57.9 months
  – Detect 20% increase 3 yr OS 54% to 65%
RTOG 0424: HRG2 Temodar+XRT

- 136 Patients

Eligibility
Supratentorial LGG
3-5 High Risk Factors
  - Age ≥40
  - Astrocytoma
  - ≥6 cm
  - Midline cross
  - Neurologic deficits before surgery

3D 54Gy/1.8 Radiotherapy + Concurrent 75/m² Temodar

150-200 mg/m²/day days 1-5 q28 days for up to 12 cycles

ASCO 2013
Results

- Median FU 4.1y (3y minimum)
- Median OS not reached
- Median PFS – 4.5 years

Overall Survival

EORTC

Expected

RTOG0424

P<0.0001

NS:3 vs. 5 risk factors
Temozolomide chemotherapy versus radiotherapy in molecularly characterized (1p loss) low-grade Gliomas: A randomized phase III intergroup study by the EORTC/NCIC-CTG/TROG/MRC-CTU (EORTC 22033-26033)

- **Goal:** To assess primary chemotherapy in HR LGG vs. conventional RT for PFS and OS

- **Eligibility**
  - Progressive or HR LGG
  - KPS ≥60

- **Randomized Stratification**
  - 1p-status

- **Chemotherapy**
  - ddTMZ (75 mg/m² daily x 21 days, q28 days, max. 12 cycles)
  - N=226

- **Radiotherapy**
  - RT (54 Gy/1.8 Gy per fraction by week 8)
  - N=221

J Clin Oncol 31, 2013 (suppl; abstr 2007)
<table>
<thead>
<tr>
<th></th>
<th>RT (n=240)</th>
<th>TMZ (n=237)</th>
<th>TMZ vs RT HR (CI), p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median, range)</td>
<td>44 yrs (18-72)</td>
<td>45 yrs (19-75)</td>
<td></td>
</tr>
<tr>
<td>WHO PS 0-1</td>
<td>95%</td>
<td>97%</td>
<td></td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Astrocytoma/Oligoastro.</td>
<td>36 / 24%</td>
<td>33 / 25%</td>
<td></td>
</tr>
<tr>
<td>Oligodendroglioma</td>
<td>39%</td>
<td>41%</td>
<td></td>
</tr>
<tr>
<td>1p Deleted</td>
<td>41%</td>
<td>41%</td>
<td></td>
</tr>
<tr>
<td>Undetermined</td>
<td>15%</td>
<td>14%</td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Debulking / complete</td>
<td>60%</td>
<td>61%</td>
<td></td>
</tr>
<tr>
<td>Biopsy</td>
<td>40%</td>
<td>39%</td>
<td></td>
</tr>
<tr>
<td>PFS (median, CI)</td>
<td></td>
<td></td>
<td>246 events</td>
</tr>
<tr>
<td>All patients</td>
<td>47 mo (40, 56)</td>
<td>40 mo (35, 44)</td>
<td>1.16 (0.9, 1.5) p=0.23</td>
</tr>
<tr>
<td>1p intact</td>
<td>41 mo (32, 55)</td>
<td>30 mo (24, 40)</td>
<td>1.41 (0.9, 2.0) p=0.06</td>
</tr>
<tr>
<td>1p deleted</td>
<td>58 mo (41, 67)</td>
<td>55 mo (38, N)</td>
<td>1.01 (0.7, 1.5) p=0.95</td>
</tr>
<tr>
<td>OS</td>
<td></td>
<td></td>
<td>108 events</td>
</tr>
<tr>
<td>All patients</td>
<td>Not reached</td>
<td>74 (69, N)</td>
<td>0.9 (0.6, 1.3) p=0.55</td>
</tr>
<tr>
<td>1p intact</td>
<td></td>
<td></td>
<td>1.03 (0.6, 1.7) p=0.9</td>
</tr>
<tr>
<td>1p deleted</td>
<td></td>
<td></td>
<td>0.47 (0.2, 1.0) p=0.05</td>
</tr>
</tbody>
</table>
What have we learned...

• HR LGG have poor prognosis should be treated as a separate entity

• RTOG 0424: First Phase II data to suggest TMZ+RT superior treatment in HR-LGG

• EORTC RND Phase III: Suggests similar outcome of TMZ alone vs RT alone

• Need more mature data to compare OS

• Sufficient data exists for RND trials