CATNON and CODEL – Update in Mx Anaplastic Glioma

Dr Rahul Krishnatry
Associate Prof. Radiation Oncology
Tata Memorial Centre, HBNI University, Mumbai

krishnatry@gmail.com
Anaplastic glioma

- About 20-30% of all newly diagnosed primary brain tumors in adults
  - Anaplastic Astrocytoma,
  - Anaplastic Oligoastrocytoma
  - Anaplastic Oligodendroglioma.

Diffuse Adult Glioma

Low Grade Glioma
G 1-2

High Grade Glioma
G 3-4
3: Anaplastic
4: GBM

Subtypes Path micro: Pure Oligo/Astro/Mixed (Gr 1-3)
Anaplastic glioma

• Traditionally treated similar to GBM
  • Maximum safe resection followed by RT (60Gy EQD2) with TMZ f/b adj TMZ 6 cycles or similar regimens as per institutional choices
    • RT alone
    • RT & concurrent CT
    • RT + adjuvant CT
    • RT & concurrent CT + adjuvant CT
  • CT: PCV variations to TMZ

• Reason for lack of clarity / consensus
  • Heterogeneous group
    • Pathologically: Astrocytoma, Oligodendroglioma, Mixed (AA, AO, AOA)
    • Biologically: IDH, 1p19q, MGMT, PTEN, P53 etc
    • Clinical outcomes 2 years median values to 12-15 years PFS / OS
      • Vary from grade to GBM outcomes.
Objectives:

- Briefly discuss historical data:
  - EORTC 26951 & RTOG 9402

- Latest studies available outcomes and their implication on current practice:
  - CATNON & CODEL
• To assess whether concurrent radiotherapy with daily temozolomide chemotherapy improves overall survival as compared to no daily temozolomide in non-1p/19q deleted anaplastic glioma.

• To assess whether adjuvant temozolomide chemotherapy improves survival as compared to no adjuvant temozolomide chemotherapy in non-1p/19q deleted anaplastic glioma.
EORTC study 26951

Anaplastic ODG: RT alone 59.4 Gy vs RT f/b 6 adj std PCV

Median follow-up of 140 months

PFS

24.3 vs 13.2 m
HR, 0.66; 95% CI, 0.52 to 0.83

OS

42.3 vs 30.6 m
HR: 0.75; 95% CI, 0.60 to 0.95

DOI: 10.1200/JCO.2012.43.2229
EORTC study 26951

1p/19q-codeleted tumors

- 157 v 50 months
- HR, 0.42; 95% CI, 0.24 to 0.74

PFS

non-1p/19q-codeleted tumors

- 15 v 9 months
- HR, 0.73; 95% CI, 0.56 to 0.97

DOI: 10.1200/JCO.2012.43.2229
EORTC study 26951

A. 1p/19q-codeleted tumors

- Treatment:
  - RT
  - RT/PCV

- Percent:
  - 100 (at 0)
  - 90, 80, 70, 60, 50, 40, 30, 20, 10, 0 (at 14 years)

- Time (years):
  - 0
  - 2
  - 4
  - 6
  - 8
  - 10
  - 12
  - 14

- Not reached v 112 months
- HR, 0.56; 95% CI, 0.31 to 1.03

- P = .059

B. non-1p/19q-codeleted tumors

- Treatment:
  - RT
  - RT/PCV

- Percent:
  - 100 (at 0)
  - 90, 80, 70, 60, 50, 40, 30, 20, 10, 0 (at 16 years)

- Time (years):
  - 0
  - 2
  - 4
  - 6
  - 8
  - 10
  - 12
  - 14
  - 16

- 25 v 21 months
- HR, 0.83; 95% CI, 0.62 to 1.10

- P = .185
RTOG 9402

AO/AOA: intense PCV f/b RT versus RT alone.

Whole Cohort OS

- Assessed for eligibility: 239 patients
- Excluded: 6 patients
- Ineligible histology: 3 patients
- Central pathology not documented: 2 patients
- Other reasons: 3 patients

Patients randomly assigned: 231 patients

- Allocated to PCV + RT: 148 patients
  - Received allocated intervention: 148 patients
  - Did not receive allocated intervention: 0 patients

- Allocated to RT alone: 143 patients
  - Received allocated intervention: 140 patients
  - Did not receive allocated intervention: 3 patients
  - Progression: 1 patient
  - Other: 2 patients

Overall Survival (%)

Time Since Random Assignment (years)

Dead
Total

PCV + RT
RT

140
148
113
143

4.6 v 4.7 yrs

Codel OS

- Dead
Total

PCV + RT
RT

28
59
47
67

14.7 v 7.3 years

DOI: 10.1200/JCO.2012.43.2674
RTOG 9402

AO/AOA: intense PCV f/b RT versus RT alone.

Whole Cohort OS

Codel OS

Non-codel

4.6 v 4.7 yrs

14.7 v 7.3 years
RTOG 9402

AO/AOA: intense PCV f/b RT versus RT alone.

Whole Cohort

RT alone
Diffuse Adult Glioma: 2016 WHO update
Issues with PCV: Toxicity

- **RTOG:**
  - PCV
    - Lomustine 130 mg/m² PO D1
    - Procarbazine 75 mg/m² PO D8-21
    - Vincristine 1.4 mg/m² i/v D 8
  - RT + PCV: G3: 34%, G4: 32%, 1 death
  - Percentage receiving four, three, two, one, and no cycles was 54%, 22%, 9%, 12%, and 2%,
  - PCV stopped:
    - Progression or death in 17%,
    - Toxicity in 20%,
    - Other reasons in 15%.

- **EORTC:**
  - PCV
    - Lomustine 110 mg/m² PO D1
    - Procarbazine 60 mg/m² PO D 8 - 21,
    - Vincristine 1.4 mg/m² i/v D 8 & 29
  - 13% of patients randomized to RT/PCV that did not actually receive
  - 37% completed at least five cycles, and 30% completed six cycles
  - Reasons for premature discontinuation
    - Hematologic toxicity in 33%
    - Nonhematologic toxicity in 5%,
    - Tumor progression in 24%,
    - Patient refusal in 5%,
    - Other reasons in 4%. 
Lack of evidence make science into art

• Current Practice survey
  • RT only
  • RT – Adj CT
  • cCT-RT + Adj CT
  • cCT-RT only

• Variability in CT
  • PCV and its variations
  • TMZ
Diffuse Adult Glioma

- Low Grade Glioma
  - G 1-2
  - IDH non mutated Astro
  - IDH mutated Astro

- High Grade Glioma
  - G 3
  - Oligodendroglioma
    - 1p19 co del

- GBM
  - CODEL study
  - CATNON study
Intergroup Study (EORTC 26053_22054)
(EudraCT number 2006-001533-17)
(NCT00626990)

Phase III trial on Concurrent and Adjuvant Temozolomide chemotherapy in non-1p/19q deleted anaplastic glioma. The CATNON Intergroup trial.

Collaborative Groups/Co-Chairs:

- EORTC Brain Tumor Group/W. Wick, A. Omuro, R. Soffietti
- EORTC Radiation Oncology Group/ B. Baumert
- NCI-C/ J.G. Cairncross, W. Mason
- RTOG/M. Metha, M. Vogelbaum
- MRC/NCRI Brain tumor Clinical Studies Group/S. Erridge
- COGNO CTC/A. Nowak
† Institution must choose to evaluate 1p/19q LOH locally or use central facility.
‡ After registration, all material is centrally reviewed for MGMT methylation status.
* Investigators can’t randomize a patient:
<table>
<thead>
<tr>
<th></th>
<th>Hazard ratio (99·145% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjuvant temozolomide</td>
<td>0·65 (0·45–0·93)</td>
<td>0·0014</td>
</tr>
<tr>
<td>Age (&gt;50 years vs ≤50 years)</td>
<td>4·04 (2·78–5·87)</td>
<td>&lt;0·0001</td>
</tr>
<tr>
<td>WHO performance status score (&gt;0 vs 0)</td>
<td>1·36 (0·94–1·96)</td>
<td>0·0273</td>
</tr>
<tr>
<td>1p loss of heterozygosity (yes vs no)</td>
<td>1·56 (0·84–2·88)</td>
<td>0·0572</td>
</tr>
<tr>
<td>Presence of oligodendroglial elements (yes vs no)</td>
<td>1·20 (0·81–1·76)</td>
<td>0·2230</td>
</tr>
<tr>
<td>MGMT promotor methylation before randomisation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methylated vs unmethylated</td>
<td>0·49 (0·26–0·93)</td>
<td>0·0031</td>
</tr>
<tr>
<td>Indeterminate or invalid vs unmethylated</td>
<td>0·81 (0·54–1·21)</td>
<td>0·1606</td>
</tr>
</tbody>
</table>

Table 2: Cox proportional hazards model of overall survival in patients receiving adjuvant temozolomide, adjusted by baseline stratification factors
<table>
<thead>
<tr>
<th></th>
<th>Overall survival</th>
<th></th>
<th>Progression-free survival</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of deaths</td>
<td>Median (95% CI) survival (months)</td>
<td>5-year survival (95% CI)</td>
<td>Number of patients with disease progression</td>
</tr>
<tr>
<td>Received adjuvant temozolomide</td>
<td>92</td>
<td>Not reached</td>
<td>55.9% (47.2-63.8)</td>
<td>144</td>
</tr>
<tr>
<td>Did not receive adjuvant</td>
<td>129</td>
<td>41.1 (36.6-60.7)</td>
<td>44.1% (36.3-51.6)</td>
<td>200</td>
</tr>
</tbody>
</table>

Table 3: Median and 5-year overall and progression-free survival
TMZ Tolerance

• Relative dose intensity was
  • > 90% in concurrent phase
  • 92% in adj patients

• one cycle delayed
  • 74 (28%) : HT
  • 16 (6%) non HT
  • 8 (3%) both
  • 123 (47%) : NR

• Overall G 3-4 toxicity : 8–12%
  • Thrombocytopenia : 7–9%
  • GI: 1-2%
Take home message

• RT + 12 4-week cycles of adj TMZ (150–200 mg/m2 given on days 1–5) improved PFS and OS in 1p/19 non-co-deleted anaplastic glioma.
Adjuvant and concurrent temozolomide for 1p/19q non-co-deleted anaplastic glioma (CATNON; EORTC study 26053-22054): second interim analysis of a randomised, open-label, phase 3 study.
Non IDH mutated
IDH mutated
Take Home message

• TMZ given simultaneously with RT does not improve overall survival compared to RT alone

• Clinical benefit of adding adjuvant TMZ to RT is limited to patients with *IDH1* or *IDH2* mutant tumours only
Background. We report the analysis involving patients treated on the initial CODEL design. Methods. Adults (>18) with newly diagnosed 1p/19q World Health Organization (WHO) grade III oligodendroglioma were randomized to

1. RT (RT; 5940 centigray) alone (arm A); RT followed by adjuvant PCV
2. RT with concomitant and adjuvant temozolomide (TMZ) (arm B);
3. TMZ alone (arm C).

Primary endpoint was overall survival (OS), arm A versus B. Secondary comparisons were performed for OS and PFS, comparing pooled RT arms versus TMZ-alone arm.
RT alone = RT + TMZ
TMZ alone not as good as RT or RT + TMZ
<table>
<thead>
<tr>
<th>Authors</th>
<th>Study Type</th>
<th>N</th>
<th>Initial Treatment</th>
<th>Median PFS or Median TTP, y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lassman et al</td>
<td>Case Series</td>
<td>124</td>
<td>TMZ</td>
<td>3.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PCV</td>
<td>7.6</td>
</tr>
<tr>
<td>Mikkelsen et al</td>
<td>Case Series</td>
<td>36</td>
<td>TMZ</td>
<td>2.4</td>
</tr>
<tr>
<td>Thomas et al</td>
<td>Phase II</td>
<td>33</td>
<td>TMZ → ASCT</td>
<td>5</td>
</tr>
<tr>
<td>Wick et al</td>
<td>Phase III</td>
<td>17</td>
<td>TMZ</td>
<td>4.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>16</td>
<td>PCV</td>
<td>9.4</td>
</tr>
</tbody>
</table>

AO, anaplastic oligodendroglioma; AOA, anaplastic oligoastrocytoma; HDC-ASCT, high dose chemotherapy with autologous stem cell transplant; TTP, time to progression.

a1p/19q codeleted, CpG island methylator phenotype + patients.
bResponders to TMZ subsequently received ASCT.
<table>
<thead>
<tr>
<th></th>
<th>Arm A: RT Alone (N = 9)</th>
<th>Arm B: RT + Concomitant TMZ (N = 11)</th>
<th>Arm C: TMZ Alone (N = 9)</th>
<th>Total (N = 29)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median Days to Testing (range)</strong></td>
<td>87 (84–105)</td>
<td>85 (73–130)</td>
<td>82 (59–97)</td>
<td>86 (59–130)</td>
<td>0.13a</td>
</tr>
<tr>
<td><strong>Frequency of Deterioration</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HVLTR Immediate Recall, n (%)</strong></td>
<td>1 (11.1)</td>
<td>1 (9.1)</td>
<td>1 (11.1)</td>
<td>3 (10.3)</td>
<td>0.99d</td>
</tr>
<tr>
<td><strong>COWAT, n (%)</strong></td>
<td>0 (0.0)</td>
<td>1 (9.1)</td>
<td>1 (11.1)</td>
<td>2 (6.9)</td>
<td>0.20d</td>
</tr>
<tr>
<td><strong>Trail Making A, n (%)</strong></td>
<td>1 (12.5)</td>
<td>0 (0.0)</td>
<td>3 (37.5)</td>
<td>4 (15.4)</td>
<td>0.18d</td>
</tr>
<tr>
<td><strong>Trail Making B, n (%)</strong></td>
<td>5 (71.4)</td>
<td>3 (33.3)</td>
<td>3 (42.9)</td>
<td>11 (47.8)</td>
<td>0.29d</td>
</tr>
<tr>
<td><strong>HVLTR Delayed Recall, n (%)</strong></td>
<td>3 (33.3)</td>
<td>1 (9.1)</td>
<td>0 (0.0)</td>
<td>4 (14.3)</td>
<td>0.18d</td>
</tr>
<tr>
<td><strong>HVLTR Delayed Recognition, n (%)</strong></td>
<td>2 (22.2)</td>
<td>2 (18.2)</td>
<td>1 (12.5)</td>
<td>5 (17.9)</td>
<td>0.24d</td>
</tr>
<tr>
<td><strong>Progression Determination</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Neurocognitive Progression, N (%)</strong></td>
<td>7 (77.8)</td>
<td>8 (72.7)</td>
<td>6 (66.7)</td>
<td>21 (72.4)</td>
<td>0.87d</td>
</tr>
<tr>
<td><strong>Clinical Progression, n (%)</strong></td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>NA</td>
</tr>
</tbody>
</table>

RCI, reliable change index; HVLTR, Hopkins Verbal Learning Test–Revised; COWAT, Controlled Oral Word Association Test.

*RCI90 value decrease from baseline.

**Number deteriorating on any one subtest >RCI90 value decrease from baseline.

***Defined by clinical exam and/or radiographic progression at 3 months after registration.

^Chi-square.

*Kruskal–Wallis.
Take home message

• For anaplastic ODG (1p19q co del):
  • TMZ alone should be avoided.
  • RT + TMZ vs RT vs PCV is not known