GBM-PNET

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Clinical Features

• 42 yr./M
• Chief complaints
  – Headache x 6 months
  – Blurred vision x 6 months
  – Hearing difficulty x 6 months
  – Episodes of Generalised seizures x 15 days
• Known hypertensive previously on medication
• No significant family history
• No h/o any addictions
Clinical Features

- KPS -80; GCS- E4V5M6
- Cranial nerves – No deficit
- Motor
  - Tone – Normal
  - Power – 5/5 in all four limbs
  - DTR – Normal
  - Plantar response – Flexor
- Sensory – Normal
- Cerebellar signs – Absent
Imaging – T1W Post contrast
Imaging – FLAIR
Surgery

- Provisional Diagnosis – Left Temporal Glioma
- Gross Total Resection of tumour under Neurosurgery
- Intra op
  - Greyish solid cystic moderately vascular tumour with poorly defined plane with normal brain.
  - Tumour arising from temporal horn and involving atrium and occipital horn.
Histopathology

- Biphasic tumour composed of
  - Astrocytic component with increased cellularity, pleomorphism, mitoses and endothelial proliferation
  - Undifferentiated round cell component
- Immuno-histochemistry
  - Astrocytic component
    - Positive: GFAP and p53
    - Negative: IDH-1 and ATRX
  - Small cell component
    - Positive: Chromogranin, synaptophysin, NeuN, and p53
    - Negative: NF, IDH-1, GFAP and ATRX
- MIB-1 Labelling Index – 30%
Final Diagnosis

- Glioblastoma multiforme with Primitive Neuroectodermal Tumour component (GBM-PNET)
Work up

• Post op Contrast enhanced MRI Brain
  – Post operative cavity in left temporal lobe with residual disease in left hippocampal and para hippocampal region and along margin of cavity.

• MRI spine screening in view of PNET component
  – No spinal subarachnoid seeding

• Cerebrospinal fluid cytology
  – Negative

• Complete blood count/Liver function test/Kidney function test
  – Within normal limits
Plan

Adjuvant Local RT with concurrent Temozolomide

Adjuvant Temozolomide for 6 months

Follow up
Contouring – Pre op GTV

Pre-op
Post contrast
GTV

Pre-op
FLAIR
GTV
Contouring - CTV

CTV 60Gy

CTV 50Gy
IMRT-SIB plan

• Nine coplanar fields
Dose: 60 Gy/20#/4wks (PTV 60)
50 Gy/20#/4wks (PTV 50)

Orange – 57 Gy Isodose
Green – 47.5 Gy Isodose
DVH
DVH parameter - Target

- D95
  - PTV 60 = 57.5Gy
  - PTV 50 = 51 Gy
- Heterogeneity index – 1.1
- Conformity index – 1.1
## DVH parameter - OARs

<table>
<thead>
<tr>
<th>OAR</th>
<th>Constraint</th>
<th>Achieved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain stem Dmax</td>
<td>54 Gy</td>
<td>57.5 Gy ( &gt;54 Gy = 2cc)</td>
</tr>
<tr>
<td>Optic chiasm Dmax</td>
<td>50 Gy</td>
<td>53.5 Gy (&gt;50 Gy = 0.4cc)</td>
</tr>
<tr>
<td>Right Optic Nerve Dmax</td>
<td>50 Gy</td>
<td>36 Gy</td>
</tr>
<tr>
<td>Left Optic Nerve Dmax</td>
<td>50 Gy</td>
<td>47.5 Gy</td>
</tr>
<tr>
<td>Right Eye Dmax</td>
<td>45 Gy</td>
<td>27 Gy</td>
</tr>
<tr>
<td>Left Eye Dmax</td>
<td>45 Gy</td>
<td>37.8 Gy</td>
</tr>
<tr>
<td>Right Temporal lobe Dmax</td>
<td>60 Gy</td>
<td>43.6 Gy</td>
</tr>
<tr>
<td>Spinal Cord</td>
<td>45 Gy</td>
<td>4.1 Gy</td>
</tr>
</tbody>
</table>
## DVH parameter – OARs

<table>
<thead>
<tr>
<th>OAR</th>
<th>Dose received</th>
<th>Tolerance dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right Cochlea Dmean</td>
<td>15.4 Gy</td>
<td>45 Gy</td>
</tr>
<tr>
<td>Left Cochlea Dmean</td>
<td>25 Gy</td>
<td>45 Gy</td>
</tr>
<tr>
<td>Right Lacrimal Gland Dmean</td>
<td>22.3 Gy</td>
<td>25 Gy</td>
</tr>
<tr>
<td>Left Lacrimal gland Dmean</td>
<td>23.2 Gy</td>
<td>25 Gy</td>
</tr>
<tr>
<td>Right Lens Dmax</td>
<td>9.9 Gy</td>
<td>10 Gy</td>
</tr>
<tr>
<td>Left Lens Dmax</td>
<td><strong>10.4 Gy</strong></td>
<td>10 Gy</td>
</tr>
</tbody>
</table>
Review of Literature
Glioblastoma Multiforme

- Most common malignant brain tumour
  - 75% of all high grade gliomas.*
- Median survival – 14 to 24 months
- Standard of care
  - Surgery
  - Adjuvant radiotherapy with conc. Chemo and Tumour treating fields
  - Adjuvant chemotherapy

*Perez & Brady’s Principle and Practice of Radiation Oncology 6th ed.
GBM Variants

- WHO defined variants
  - Classical GBM – primary vs secondary
  - Gliosarcoma
  - Giant cell GBM

- Emerging variants*
  - Fibrillary/epithelial GBM
  - GBM with oligodendroglioma component
  - GBM with primitive neuroectodermal tumor (GBM-PNET)
  - Small cell GBM
  - Gemistocytic astrocytoma
  - Granular cell astrocytoma

GBM-PNET

- Approx. 0.5% of GBM cases
- Median age – 51 to 54 yrs.
- Male preponderance
  - M:F = 1.3
- Location
  - Most common – Temporal lobe (~50%)
  - Infratentorial – rare
- Increased risk of CSF dissemination (?)
- Median survival – 9.1 months
Primary vs Secondary GBM

**Primary glioblastoma**
- Neural, classical, mesenchymal, proneural transcriptional profiles

**Secondary glioblastoma**
- Proneural transcriptional profile
- Hypermethylation phenotype

**Primary vs Secondary GBM Flowchart**

- **Glial progenitor cells**
  - 3–6 mo clinical history
  - \( EGFR \) amplification (~35%)
  - \( TP53 \) mutation (~30%)
  - \( PTEN \) mutation (~25%)
  - LOH 10p (~50%)
  - LOH 10q (~70%)

- **Primary glioblastoma**

- **Common precursor cells with IDH1/2 mutation**
  - TP53 mutation (~65%)
  - ATRX mutation (~65%)

- **Diffuse astrocytoma**
  - ~5 y

- **Anaplastic astrocytoma**
  - LOH 19q (~50%)
  - LOH 10q (~60%)
  - ~2 y

- **Secondary glioblastoma**

- **Oligodendroglioma**
  - Loss 1p/19q (>75%)
  - CIC mutation (~40%)
  - FUBP1 mutation (~15%)

**WHO grade**
- II
- III
- IV

© 2012 American Association for Cancer Research

**Association of Residents in Radiation Oncology**
Algorithm for molecular classification

diffuse glioma

<table>
<thead>
<tr>
<th>Histology</th>
<th>Diffuse astrocytic and oligodendrogial gliomas WHO grade II or grade III</th>
<th>Diffuse astrocytic gliomas/glioblastomas WHO grade IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDH status</td>
<td>IDH-mutant</td>
<td>IDH-wild-type</td>
</tr>
<tr>
<td>ATRX status</td>
<td>Nuclear ATRX retained</td>
<td>Nuclear ATRX retained*</td>
</tr>
<tr>
<td>1p/19q status</td>
<td>1p/19q-codeleted</td>
<td>1p/19q-non-codeleted</td>
</tr>
<tr>
<td>H3-K27M status</td>
<td>Oligodendroglioma, IDH-mutant, 1p/19q-codeleted, WHO grade II or III</td>
<td>Astrocytoma, IDH-wild-type, WHO grade II or III*</td>
</tr>
</tbody>
</table>

Louis et al 2016 Acta Neuropath
Survival outcomes

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFRvIII</td>
<td>25% 23 months¹</td>
</tr>
<tr>
<td>Positive for EGFRvIII</td>
<td>45% 22 months²</td>
</tr>
<tr>
<td>Negative for EGFRvIII</td>
<td>55% 13 months²</td>
</tr>
<tr>
<td>MGMT Gene</td>
<td>50% 15 months²</td>
</tr>
<tr>
<td>Methylated MGMT</td>
<td>22 months²</td>
</tr>
<tr>
<td>Unmethylated MGMT</td>
<td>13 months²</td>
</tr>
<tr>
<td>Age</td>
<td>50% 15 months²</td>
</tr>
<tr>
<td>Under 65</td>
<td>50% 9 months²</td>
</tr>
<tr>
<td>Over 65</td>
<td></td>
</tr>
</tbody>
</table>

¹ Data based on general patient populations treated with rindopepimut immunotherapy and temozolomide and lacking a placebo control.
² Data based on patient populations receiving radiotherapy and temozolomide.

Somatic Genomic landscape of GBM

Cell 2013
Imaging

- Heterogeneously enhanced solid cystic lesion
- Mass effect
- Peritumoral edema
- Diffusion restriction in DWI
  - High cellularity of PNET component
Histopathology

- Two distinct architecture
- GBM
  - Neoplastic astrocytes
  - Necrosis
  - Nuclear atypia
- PNET foci
  - High nuclear to cytoplasmic ratio
  - Mitotic activity
  - Homer-Wright rosettes
Immuno-histochemistry

- Glial component
  - GFAP +
- PNET component
  - S100
  - Synaptophysin
  - NeuN
  - NFP

  Neuronal Markers

- Proliferative index (MIB-LI or Ki-67)
  - Glial- 10 to 40%
  - PNET- 40 to >90%
- p53 nuclear staining
  - Both Glial and neuronal component
  - ~ 83%
- N-myc amplification in PNET component
Origin

• Monoclonal origin with different differentiation pattern
  – Neuronal and glial cells of CNS originate from same stem cell
  – Neural stem cell markers CD113 and nestin found in stem cells isolated from gliomas*

• Secondary GBM
  – Younger age of onset as compared to primary GBM (62 yrs)
  – Frequent history of prior low grade gliomas
  – Strong and diffuse immunoreactivity for p53
  – Frequent IDH1 mutation
  – Rarity of EGFR amplification

Cancer Res 2015
Differentiation from other GBM 
Variants

<table>
<thead>
<tr>
<th></th>
<th>Classical GBM</th>
<th>GBM PNET</th>
<th>Small cell GBM</th>
<th>Gliosarcoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histo-pathology</td>
<td>Infiltrating pleomorphic cells, mitoses, endothelial proliferation and necrosis</td>
<td>GBM with PNET areas showing hypercellularity, Homer-Wright rosettes, small hyperchromatic nuclei</td>
<td>Monomorphic cells with small round nuclei</td>
<td>GBM along with heterogeneous sarcomatous differentiation</td>
</tr>
<tr>
<td>IHC/FISH</td>
<td>GFAP</td>
<td>GFAP Synaptophysin Chromogranin NeuN</td>
<td>EGFR amplification</td>
<td>Reticulin Vimentin Laminin Collagen IV α1-antitrypsin</td>
</tr>
<tr>
<td>Median Survival</td>
<td>14-24 months</td>
<td>9 months</td>
<td>6-14 mo</td>
<td>4-11 mo</td>
</tr>
<tr>
<td>Case series/report</td>
<td>n</td>
<td>Adjuvant RT</td>
<td>Adjuvant Chemo</td>
<td>Outcome</td>
</tr>
<tr>
<td>--------------------</td>
<td>----</td>
<td>-------------</td>
<td>----------------</td>
<td>---------</td>
</tr>
<tr>
<td>Perry et al 2009</td>
<td>53</td>
<td>Local RT (17) CSI (1) Concurrent chemo (1)</td>
<td>Temozolomide/ BCNU (16)* Platinum based (3)</td>
<td>Median Survival – 9.1 mo Local progression – all CSF dissemination – 21%</td>
</tr>
<tr>
<td>Song et al 2011</td>
<td>10</td>
<td>Local RT (9)</td>
<td>Temozolomide (10)</td>
<td>Median Survival – 10 mo CSF dissemination – 20%</td>
</tr>
<tr>
<td>Lee et al 2012</td>
<td>3</td>
<td>Local RT 60 Gy with Temozolomide and Carboplatin</td>
<td>Ifos+Carbo+Eto → Temozolomide</td>
<td>1 local progression at 32 mo 2 disease free at 36 and 56 mo</td>
</tr>
<tr>
<td>Kaplan et al 2007</td>
<td>1</td>
<td>Local RT</td>
<td>NA</td>
<td>Local progression – 10 mo</td>
</tr>
<tr>
<td>Kandemir et al 2009</td>
<td>1</td>
<td>Local RT</td>
<td>NA</td>
<td>No recurrence at 9 mo</td>
</tr>
<tr>
<td>Chu et al 2015</td>
<td>1</td>
<td>Local RT 59.4 Gy → 17Gy SRS boost</td>
<td>Temozolomide</td>
<td>Local progression – 1 mo Survival – 28 mo</td>
</tr>
</tbody>
</table>
Adjuvant Treatment

• Local Radiotherapy
  – Similar to GBM
  – Dose 60 Gy

• CSI
  – Controversial
  – Rarely used in retrospective series
  – Local failure most common

• Chemotherapy
  – Temozolomide
  – Platinum based chemotherapy who fail on temozolomide and RT.
Conclusion

• Rare entity
• Monoclonal origin from secondary GBM
• Biphasic tumour in histopathology, IHC to differentiate from GBM
• Prognosis similar to GBM
• Adjuvant treatment in line of GBM
Literature on GBM
GBM Standard: EORTC/NCIC Trial

- Age <= 70
- 574 pts randomized 1:1
  - 60 Gy
  - 60 Gy/TMZ → TMZ
- Improved median survival
  - 12.1 → 14.6 months
  - P<0.001

MGMT methylated confers better outcomes

- DNA repair by O6-methylguanine methyltransferase
- Resistance to alkylating agents
- Prognostic and predictive significance

Hegi M, et al. JCO 2008
IDH mutated GBM does better

- IDH mutations are earliest detectable genetic alterations in precursor LGG
- Primary GBM = IDH wt
  - Secondary GBM = IDH mut
- Prognostic but not necessarily predictive

Zou P et al. PLOS One 2013
Sanson M et al. JCO 2009
• KPS ≥ 70; median age 56
• 695 pts randomized 2:1 after 60 Gy/TMZ
  • Adjuvant TMZ + TTFields
  • Adjuvant TMZ
• Improved median survival (from time of randomization)
  • 16.0 → 20.9 months
  • P<0.001
• Toxicity
  • Skin toxicity in 52%
Tumor-Treating Fields

• HRQOL data
• Same global health status

Methylated GBM: CeTeG/NOA-09 Trial

- 129 patients with MGMT methylation and age ≤ 70
- Randomized 1:1

Methylated GBM: CeTeG/NOA-09 Trial

- Age ≤ 70 (median age 58, 61% GTR)
- 129 pts randomized 1:1
  - 60 Gy/TMZ → 6 cycles TMZ
  - 60 Gy/6 cycles TMZ & CCNU
- Improved median survival
  - 31.4 → 48.1 months
  - P=0.0492
- Based on stratified log rank test, not significant on Cox regression analysis
- No effect on PFS (?pseudopropgression)

Methylated GBM: CeTeG/NOA-09 Trial

Table 2: Grade 3 events 51% → 59%

<table>
<thead>
<tr>
<th>Haematological events</th>
<th>Temozolomide (n=63)</th>
<th>Lomustine-temozolomide (n=66)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All grades</td>
<td>Grade 3 or 4</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>10 (16%)</td>
<td>8 (13%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>7 (11%)</td>
<td>4 (6%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>19 (30%)</td>
<td>15 (24%)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>4 (6%)</td>
<td>4 (6%)</td>
</tr>
<tr>
<td>Anaemia</td>
<td>3 (5%)</td>
<td>3 (5%)</td>
</tr>
</tbody>
</table>

GBM Standard

2005: Temozolomide

2015: Tumor treating fields


Stupp R et al. JAMA 2017
GBM ongoing trials for upfront treatment

Randomized
- Nivolumab vs TMZ for unmethylated: CheckMate 498
- Placebo/TMZ vs nivolumab/TMZ: CheckMate 548
- Antibody drug conjugate to EGFR (depatuxizumab mafodotin: ABT-414) vs placebo: M13-813/RTOG 3508
- Dose escalation to TMZ/75 Gy/30 fx vs TMZ/60 Gy: NRG BN001
Elderly GBM: Canadian Study “Roa”

- Age > 60
- 40 Gy in 15 = 60 Gy in 30
  - 5.6 vs 5.1 months median survival
  - P=0.57
- No temozolomide

Roa et al. J of Clin Oncol 2004
Elderly GBM: Nordic Trial

• Age > 60
• 60 Gy worse than 34 Gy/10 or TMZ alone
• Methylated MGMT associated with better survival for TMZ
  • Did not matter for RT

Elderly GBM: NOA-08

- Age > 65, KPS > 60
- TMZ = 60 Gy RT
  - 8.6 vs 9.6 mo median survival
- MGMT- benefited from RT not TMZ
- More toxicity with TMZ

Elderly GBM: CCTG/EORTC/TROG

- Age ≥ 65, ECOG PS 0-2
- 40 Gy/TMZ → better
  - 9.3 vs 7.6 mo median survival
  - p<0.001
- Benefit mostly for MGMT+ but also in MGMT-
  - ?whether methylation is most accurate test of MGMT

GBM standard: Contouring guidelines

<table>
<thead>
<tr>
<th>RTOG</th>
<th>EORTC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>46 Gy in 23 fractions</strong></td>
<td><strong>60 Gy in 30 fractions</strong></td>
</tr>
<tr>
<td>GTV1 = surgical cavity + residual enhancing tumor + <em>surrounding edema</em></td>
<td>GTV = surgical resection cavity + residual enhancing tumor</td>
</tr>
<tr>
<td>CTV1 = GTV1 + 2 cm</td>
<td>CTV = GTV + 2 cm</td>
</tr>
<tr>
<td><strong>14 Gy in 7 fractions</strong></td>
<td></td>
</tr>
<tr>
<td>GTV2 = surgical cavity + residual enhancing tumor</td>
<td><em>In RTOG 0525 and CENTRIC trials, no difference in OS between EORTC and RTOG sites</em></td>
</tr>
<tr>
<td>CTV2 = GTV2 + 2 cm</td>
<td></td>
</tr>
</tbody>
</table>

*In RTOG 0525 and CENTRIC trials, no difference in OS between EORTC and RTOG sites*

## GBM: Smaller margins?

<table>
<thead>
<tr>
<th>Center</th>
<th>n</th>
<th>Initial</th>
<th>Boost</th>
<th>Infield recurrence</th>
<th>OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emory</td>
<td>62</td>
<td>CTV=T2 + 0.7cm</td>
<td>PTV=T1 gad/cavity + 0.5 cm</td>
<td>93%</td>
<td></td>
</tr>
<tr>
<td>McDonald MW et al. Int J Radiat Oncol Biol Phys 2011</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alabama</td>
<td>95</td>
<td>PTV=T2+ 1 cm</td>
<td>PTV=T1 gad/cavity + 0.5 cm</td>
<td>81%</td>
<td></td>
</tr>
<tr>
<td>Gebhardt BJ et al Radiat Oncol 2014</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wake Forest</td>
<td>29</td>
<td>0.5 cm</td>
<td></td>
<td></td>
<td>No difference</td>
</tr>
<tr>
<td>Paulsson AK et al Am J Clin Oncol 2014</td>
<td>78 38</td>
<td>1 cm 1 cm 1-2 cm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iowa</td>
<td>191</td>
<td>PTV=T2+ 0.4-1 cm</td>
<td>PTV=T1 gad/cavity + 0.4-1.0 cm</td>
<td></td>
<td>16.1</td>
</tr>
<tr>
<td>Guram K et al IJROBP 2018</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Pseudoprogression

- One month post-chemoradiation
  - Half are bigger
  - 2/3 turn out to be pseudoprogression
  - If pseudoprogression, 2/3 have methylated MGMT
  - If early progression, 90% have unmethylated MGMT

Brandes et al. JCO 2008
Pseudoprogression

- pSPD associated with better survival (p=0.045)
- Unclear if psPD is a marker for better prognosis (mostly methylated patients) or leads to better prognosis

Brandes et al. JCO 2008
RANO: Response Assessment in Neuro-Oncology Criteria

• Call progression within 3 months of radiation therapy ONLY if:
  • New enhancement is beyond 80% isodose line
  • Unequivocal pathologic evidence of viable tumor

Wen PY et al. JCO 2010
### RANO after 3 months

<table>
<thead>
<tr>
<th>RANO Criteria</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1 enhancing</td>
<td>None</td>
<td>≥ 50%</td>
<td>&lt; 50% if ↓ but &lt; 25% if ↑</td>
<td>≥ 25% ↑</td>
</tr>
<tr>
<td>disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2/FLAIR</td>
<td>Stable / improved</td>
<td>Stable / improved</td>
<td>Stable / improved</td>
<td>Stable / improved</td>
</tr>
<tr>
<td>New lesion</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Present</td>
</tr>
<tr>
<td>Corticosteroid use</td>
<td>None</td>
<td>Stable or ↓</td>
<td>Stable or ↓</td>
<td>NA</td>
</tr>
<tr>
<td>Clinical status</td>
<td>Stable / improved</td>
<td>Stable / improved</td>
<td>Stable / improved</td>
<td>Declined</td>
</tr>
</tbody>
</table>

Summary: GBM

• <70 yo, good KPS
  • 60 Gy/TMZ → TMZ (Stupp 2005)
  • Consider TTFields (Stupp 2017)
  • Consider CCNU/TMZ for select patients with methylated MGMT (Herrlinger 2019)
  • Consider clinical trials

• ≥70 yo, good KPS
  • 40 Gy/TMZ → TMZ (Perry 2017)

• Poor KPS
  • Consider RT alone, TMZ alone, or best supportive care (Wick 2012, Malstrom 2012, Roa 2004 and 2015)

• Unknowns
  • Target volumes
  • Ongoing experimental agents
Resources

- ASTRO refresher course
- Previous ARRO cases

Thanks!