A221208: Phase II Randomized Study of Bevacizumab vs. Steroids (BeSt) for Radionecrosis after Radiosurgery for Brain Mets

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ALLIANCE A221208: Phase II Randomized Study of Bevacizumab vs. Steroids (BeSt) for Radionecrosis after Radiosurgery for Brain Mets

Study Co-Chairs: Caroline Chung
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Normand Laperriere

Med Onc Co-Chair: Glenn Lesser
Community Oncology Co-Chair: Christopher Goulet

Neurosurgery Co-Chair: Ian Parney
Neuroradiology Imaging Co-Chair: Tim Kaufmann
Health Outcomes Co-Chair: Terri Armstrong

Biomarkers Correlative Co-Chairs: Erik Sulman
David Grosshans
Background

- ~ 10-30% patients develop brain radionecrosis following SRS
- Incidence of brain radionecrosis is rising
  - Longer survival
  - Rising cumulative RT dose with higher dose initial RT and increased reirradiation
  - Rising use of SRS

- Corticosteroids are effective, but not for all patients
- Prolonged corticosteroids can be associated with ++ toxicity

RTOG 90-05: Dose-Escalation Study

156 adults with solitary recurrent non-brainstem tumors with max diameter 4cm
- 36% primary (median prior dose 60 Gy)
- 64% brain mets (median prior dose 30 Gy)

Increased risk of grade 3-5 neurotoxicity (MVA) associated with:
- Tumor size: 21-40 mm 7.3 – 16X risk vs. <20 mm
- Tumor dose
- Karnofsky Performance Status

<table>
<thead>
<tr>
<th>Maximum Tolerated Dose</th>
<th>Maximum Tumor Diameter</th>
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<tbody>
<tr>
<td>24 Gy</td>
<td>&lt;20 mm</td>
</tr>
<tr>
<td>18 Gy</td>
<td>21-30 mm</td>
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<tr>
<td>15 Gy</td>
<td>31-40 mm</td>
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Actuarial incidence of radionecrosis:
- 5% (6mo), 8% (12 mo), 9% (18mo), and 11% (24mo)

## Risk Factor: Volume of SRS

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Incidence</th>
<th>Risk Factor</th>
<th>Risk %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minniti (2011)</td>
<td>206 pts 310 lesions</td>
<td>14% S-RN 10% A-RN</td>
<td>V10 Gy &gt; 12.6 cm³ V12 Gy &gt; 10.9 cm³</td>
<td>47% 47%</td>
</tr>
<tr>
<td>Blonigen (2010)</td>
<td>63 pts 173 lesions LINAC</td>
<td>10% S-RN 4% A-RN</td>
<td>V10 Gy 2.2-6.3 cm³ 6.4-14.5 cm³ V12 Gy 1.6-4.7 cm³ 4.8-10.8 cm³</td>
<td>11.9% 34/6% 11.9% 34.6%</td>
</tr>
<tr>
<td>Korytko (2006)</td>
<td>129 pts 198 lesions</td>
<td>V12 Gy 0-5cc V12 Gy 5-10 cc V12 Gy &gt; 15cc</td>
<td>23% 20% 54%</td>
<td></td>
</tr>
<tr>
<td>Ohtakara (2012)</td>
<td>57 pts 131 lesions LINAC</td>
<td>8.4% S-RN 6.9% A-RN</td>
<td>V12 Gy V 22 Gy (no prior WBRT)</td>
<td></td>
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</table>
Diagnostic Dilemma

Limitations of Radiological Evaluation
- Radiological appearance of brain tumours and brain radionecrosis can be very similar

Limitations of Pathological Confirmation
- Fails to have 100% sensitivity or specificity
  - Spatial heterogeneity
  - Presence of both tumor cells (which may or may not be viable) and necrosis
- Invasive procedure with additional risks to the patient
Conventional MRI

Conventional radiographic features achieved > 80% predictive value but low sensitivity/specificity:

- AV shunting
- Gyriform lesion/edema
- Enhancement pattern “cut green pepper”
- Cyst formation
Pathophysiology of Brain Radionecrosis

Endothelial cell loss

Disruption of BBB

Vasogenic edema and vascular compromise

Release of vasoactive proteins VEGF

Hypoxia “nutritional” deficiency

Necrosis

Bevacizumab
Current Management of Radionecrosis

- CORTICOSTEROIDS
  - Lesion is unresectable due to location
- HYPERBARIC OXYGEN
- BEVACIZUMAB*
  - Patient is inoperable due to rapid deterioration
- SURGICAL RESECTION

*Small studies of bevacizumab for radionecrosis show radiological and clinical response$^{2-4}$
Hypothesis

- Hypothesis: Bevacizumab will provide greater clinical and radiological improvement resulting in greater improvement in the severity of symptoms, neurological and cognitive impairment compared to conservative management with corticosteroids.
Study Schema

Randomized phase II study of bevacizumab vs. steroid therapy in patients diagnosed with radionecrosis following radiosurgery.  

N= 130, 65 per arm

Symptomatic brain radionecrosis requiring corticosteroids following SRS for brain metastases

Stratified for:
- Age
- pathological confirmation
- baseline MDASI
- prior WBRT

Central Imaging review

Bevacizumab 10 mg/kg IV days 1 and 15 for 1 cycle (30 days) x 4 cycles + corticosteroids

Cross-over allowed at progression

Placebo IV days 1 and 15 for 1 cycle (30 days) x 4 cycles + corticosteroids

FU every 2 months (up to 6 months): MR brain + clinical visit with PRO

After 6 months: event monitoring only

Drug is provided
Eligibility

Inclusion Criteria

- Symptomatic brain radionecrosis defined by onset of symptoms at 3-24 months post-SRS that requires steroid intervention and meets the following radiological criteria:
  - Lesion quotient < 0.3 ¹ OR
  - DSC ²- At least 1:
    - rCBV <1.5
    - PSR ≥ 76%

- Life expectancy > 6 months
- KPS ≥ 60%
- Acceptable organ function (bone marrow, renal, liver

Exclusion Criteria

- Acute intracranial/intratumoral hemorrhage
- Glioma or brain mets from melanoma, RCC
- Non-approved systemic therapies: 2 wks prior to registration or planned < 1 mo after registration

Except: Maintenance herceptin or hormonal therapies OR ‘Approved systemic’ therapies [Appendix]

Standard C/I to bevacizumab:
- Major surgical procedure within 28 days or core biopsy within 7 days
- Pregnant or nursing
- PT INR >1.5
- Bleeding diathesis, coagulopathy, non-healing wound/ulcer, bowel obstruction/fistula/GI perforation
- Significant cardiovascular disease
- Central lung met with xs active bleeding

¹Kumar – Radiology 2000
² Barajas – AJNR 2009
Radionecrosis & Conventional Imaging: Lesion Quotient

LQ > 0.6 in tumor

LQ < 0.3 in 80% of radionecrosis

LESION QUOTIENT = maximal cross-sectional area of T2-w hypointensity
maximal cross-sectional area of T1-gad enhancement

Kumar – Radiology 2000
Radionecrosis & Perfusion Imaging

Eligibility Criteria:
- $rCBV < 1.5$
- $PSR > 76\%$

Radionecrosis

Tumor

Table 3: Sensitivity and specificity for the detection of radiation necrosis using PSR, rCBV, and rPH values*

<table>
<thead>
<tr>
<th>Statistic</th>
<th>PSR COV = 76.3</th>
<th>rCBV COV = 1.54</th>
<th>rPH COV = 0.69</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>95.65</td>
<td>91.30</td>
<td>86.96</td>
</tr>
<tr>
<td>Specificity</td>
<td>100.00</td>
<td>72.73</td>
<td>45.45</td>
</tr>
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</table>

*COV indicates cutoff value.
*All data are presented as percentages.
Endpoints

- **Primary Endpoint**
  - Improvement in patient-reported symptoms measured by MDASI-BT global symptom score (baseline then weeks 2, 4, 6, and 8)

- **Secondary Endpoint(s)**
  - Toxicities: CTCAE version 4.0 & DSQ-C
  - QoL: LASA, MDASI-BT symptoms and interference scores
  - PFS (progression = restart higher dose steroids or alternative tx)
  - Time to maximum radiographic response
  - Corticosteroid requirements

- **Correlative Endpoints:**
  - **Biofluid Biomarkers:** angiogenic factors:
    - Angiogenic markers: VEGF-A, B, C, D, angiopoietin-1 and 2, PDGF
    - Inflammatory cytokines (TNF-α, TGF-β, IL1, and IL6)
    - Genetic markers (Apo E)
  - **Imaging Biomarker Measures:** DWI (ADC), DCE (Ktrans, iAUC)
Amendment

- Real-time central review: OPTIONAL
  - Need to submit images for secondary analysis

- Correlative biomarker studies are optional for institution and patient

- Drug administration cost language clarified
Highlights

- Drug provided for initial randomization & cross-over
  - *All patients who clinically need bevacizumab will receive it on study*

- Contact: cchung3@mdanderson.org
Conclusion

- Questions from Audience
- Answers from Presenter