Surgical Clinical Trials for High Grade Gliomas

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Outline

- High grade glioma and glioblastoma overview, standard therapies
- Extent of surgical resection and fluorescence-guided surgery
- Overview of neurosurgical trials in high grade glioma and glioblastoma
- Current experience with intratumoral convection enhanced delivery therapies at PNI and JWCI

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Introduction

- Glioblastoma is the most common primary brain tumor

- Incidence highest in patients 45-55 years old – “prime of life”

- Median survival 15 months with best current therapy involving surgery and chemoradiation (1-5% survive three years after diagnosis)

- Hallmarks of tumor:
  - Aggressive, infiltrative growth and vasogenic edema
  - Necrosis
  - Microvascular proliferation
### Benefit of Complete Microsurgical Resection

<table>
<thead>
<tr>
<th>Study</th>
<th>Extent of Resection</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Complete</td>
<td>Subtotal</td>
<td>Biopsy</td>
<td></td>
</tr>
<tr>
<td>EORTC 26981¹</td>
<td>14.2 months</td>
<td>11.7 months</td>
<td>7.8 months</td>
<td></td>
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<tr>
<td>Median OS with RT alone</td>
<td>15.0%</td>
<td>9.4%</td>
<td>4.6%</td>
<td></td>
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<tr>
<td>2-year survival with RT alone</td>
<td>18.8 months</td>
<td>13.5 months</td>
<td>9.4 months</td>
<td></td>
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<tr>
<td>Median OS with RT + temozolomide</td>
<td>38.4%</td>
<td>23.7%</td>
<td>10.4%</td>
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</tr>
<tr>
<td>2-year survival with RT + temozolomide</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>5-ALA²</td>
<td>16.9 months</td>
<td>11.8 months</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Median OS</td>
<td></td>
<td>26%</td>
<td>7%</td>
<td>–</td>
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<tr>
<td>2-year survival</td>
<td></td>
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</tbody>
</table>

Consensus that maximal safe resection is goal even when full resection not possible is reflected across guidelines

1 - Stupp et al *Lancet Oncology* 2009  
2 - Stummer et al *Neurosurgery* 2008
Fluorescence-Guided Surgery (FGS)

- Improved intraoperative visualization in real-time
- Permits more extensive resection of malignant brain tumors with infiltrative biology
- Permits safer resection of eloquent malignant brain tumors in combination with intraoperative motor and language mapping
- Impacts overall survival and has potential to reduce neurologic deficits
## GBM MGMT Methylation and Chemoradiation Response

<table>
<thead>
<tr>
<th></th>
<th>Median</th>
<th>2-yr</th>
<th>3-yr</th>
<th>4-yr</th>
<th>5-yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>MGMT unmethylated TMZ</td>
<td>12.6 mos</td>
<td>14.8%</td>
<td>11.1%</td>
<td>11.1%</td>
<td>8.3%</td>
</tr>
<tr>
<td>RT only</td>
<td>11.8 mos</td>
<td>1.8%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>MGMT methylated TMZ</td>
<td>23.4 mos</td>
<td>48.9%</td>
<td>23.1%</td>
<td>23.1%</td>
<td>13.8%</td>
</tr>
<tr>
<td>RT only</td>
<td>15.3 mos</td>
<td>23.9%</td>
<td>7.8%</td>
<td>7.8%</td>
<td>5.2%</td>
</tr>
</tbody>
</table>

Stupp et al Median OS MGMT-M 23.4 mos vs. MGMT-UM 12.6 mos
Summary of Current GBM Therapies

- Microsurgical resection is beneficial
  - Goal is maximum safe cytoreduction
  - Molecular profiling of tissue for targeted therapy selection

- Radiotherapy with concurrent and adjuvant Temozolomide is the standard of care
  - Maintenance Temozolomide x 6-12 months after RT

- Bevacizumab can be used at 1st Failure
- Novo-TTF is approved for recurrent GBM
- Consider rechallenge with Temozolomide and Re-Irradiation (ERRT, SRS)
- **Clinical Trials**: Targeted Therapies, Immunotherapies, Intratumoral Therapies

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Neurosurgical Trials in HGG and GBM

- Biological
  - Gene Therapy
    - Viral Vectors
    - Synthetic Vectors
  - Immunomodulation
    - Immunotoxins
    - Immunostimulation
    - Cell-Based Immune Therapies

- Nonbiological
  - Chemotherapy
    - Implant
    - Device-Assisted Infusion
  - Thermal
    - Nanoparticle-Based
    - Stereotactic Laser
  - Radiation
    - Brachytherapy
    - Nanoparticle Augmentation
    - Photodynamic Therapy

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Convection-Enhanced Delivery Experience at JWCI and PNI

Figure 1: Schematic of MDNA55 Mechanism of Action
MDNA55: A TARGETED DUAL-ACTION IMMUNOTHERAPEUTIC

Drug Profile And Prior Clinical Studies At A Glance

Convection-Enhanced Delivery (CED) of MDNA55 in Adults With Glioblastoma at First Recurrence or Progression

What Features Render MDNA55 A Rational Choice For Treatment Of Recurrent Glioblastoma?

- MDNA55 is a dual-action immunotherapeutic agent targeting the interleukin-4 Receptor (IL-4R)
- A majority of brain tumors, especially recurrent glioblastoma (RGB), substantially over-express IL-4R, a target that is not expressed in normal brain
- MDNA55 is directly cytotoxic to GB cells and tumor initiating stem cells through specific targeting of IL-4R
- GB has a robust immunosuppressive tumor microenvironment (TME) comprised of Tumor Associated Macrophages (TAMs) and Myeloid Derived Suppressor Cells (MDSCs) which over-express IL-4R
- IL-4R is essential for the immunosuppressive function of TAMs and MDSCs in GB patients
- By purging the TME, MDNA55 also acts as an immunotherapeutic agent as it un-blinds the immune system to GB cells
- Unlike Temozolomide and other alkylating agents, MGMT positive cancer cells are sensitive to MDNA55
- Pro-apoptotic domain of MDNA55 is far more potent than chemotherapeutic agents
- The blood brain barrier (BBB) blocks transport of systemic or orally delivered drugs to the brain tumor
- MDNA55 by-passes the BBB as it is delivered directly into the tumor using a minimally invasive method called Convection Enhanced Delivery (CED)
- CED enables accumulation of a high concentration of MDNA55 in the tumor and the TME while limiting systemic toxicity
- Precision CED technology ensures accurate catheter placement, allows real-time monitoring and optimizes drug distribution by using novel catheters thereby improving the efficacy and safety profile of MDNA55

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Patient #1: Segmented Tumor and Clinical Target
Patient #1: Catheter Placement Plan
Patient #1: Pre-Op IV Contrast vs. Intra-op CED Distribution
Patient #2: Segmented Tumor and Clinical Target
Patient #2: Catheter Placement Plan
Patient #2: Pre-Op IV Contrast vs. Intra-op CED Distribution
Patient #3: Segmented Tumor and Clinical Target
Patient #3: Catheter Placement Plan
Patient #3: Catheter Placement Plan (CT hardware avoidance)
Patient #3: Pre-Op IV Contrast vs. Intra-op CED Distribution
Summary

- New treatment approaches are required for GBM involving maximizing surgical resection and targeting remaining infiltrative cancer cells due to high local recurrence

- Use of adjuvant therapies will remain essential for providing tumor control and prevention of relapse

- Other novel therapies such as immunotherapy and intratumoral convection-enhanced delivery will also play an important role in GBM management