New Treatment Approaches for Glioblastoma

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Disclosures

- NIH/NCI Grants
- Meditech (consultant)
- Nx Development Corp. (Intellectual Property Fees; Research grant)
Outline

• GBM overview and standard therapies
  – Newly diagnosed and recurrent

• Extent of surgical resection

• Fluorescence-guided surgery of GBM
  – Phase II 5-ALA study at Winship Cancer Institute

• Targeted therapy of GBM
  – Magnetic nanoparticle treatment of GBM
  – Spontaneous canine glioma trial at UGA

Glioblastoma (GBM)

• Most common malignant primary brain tumor in adults
  – Most common malignant glioma (includes anaplastic astrocytomas)

• ~10,000-15,000 cases/yr of GBM in US

• Median survival <15 mos. despite surgery, chemo, and irradiation
  – 1-5% survive 3 years after dx
  – Radioresistant and chemoresistant

• Metastases rare, local recurrence common
**GBM Standard of Care Treatment**

European Organization for the Research and Treatment of Cancer (EORTC)/National Cancer Institute of Canada (NCIC) Treatment Platform

- **Radiotherapy (RT):** Focal, 60 Gy in 6 wk to tumor volume plus 2- to 3-cm margin
- **Temozolomide (TMZ):**
  - During RT: 75 mg/m²/d (including weekends) for up to 49d; administered 1–2 h before RT in AM on days without RT
  - Maintenance: 150–200 mg/m²/d x 5d, for up to 6 cycles; antiemetic prophylaxis

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**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
Recurrent GBM

Bevacizumab and CPT-11

Optional Post-PD Phase
Bevacizumab + CPT-11

GBM Randomized by 1st or 2nd Relapse

Bevacizumab 10 mg/kg

Bevacizumab 10 mg/kg
CPT11 EIAED 340 mg/m²
and Non-EIAED 125 mg/m²

Agent(s) Used

No. of Patients

Toxicity

CR/ORR

PFS-6

Freidman et al. 2009

Bevacizumab

85

45%*

ORR = 28%

PFS-6 = 43%

Bevacizumab

82

63%*

ORR = 38%

PFS-6 = 50%

Kriesl et al. 2009

Bevacizumab

48

57%

29%

Recurrent GBM

NovoTTF-100A: Phase III Study Design

Patients with rGBM (no limitations on prior therapies)

NovoTTF (n=120)

Best physicians’ choice* (n=117)

– Stratification: surgery for recurrence and center

– NovoTTF: continuous administration for >20 hours/day

– Primary endpoints: OS, feasibility, and toxicity

– Secondary endpoints: PFS6, TTP, QOL, 1-year OS, and ORR

*Best physicians’ choice suggested per protocol: re-exposure TMZ; PCV, procarbazine, platinum based; CCNU or BCNU. Often given per local practice: bevacizumab (+irinotecan).
Thermotherapy of Recurrent GBM

- Intratumoral injection of aminosilane-coated IONPs (core 12 nm) in 59 human patients
  - Application of AMF (100 kHz) in several sessions before and after radiation therapy
- Improved overall survival
- Median peak temperature in tumor was 51.2 °C
- MagForce Nanotherapy received European and German approval (BfArM) in 2013

Maier-Hauff et al. J Neurooncol 2011
Summary of Current GBM Therapies

- Surgery at presentation is beneficial
  - Goal is maximal safe resection
  - Carmustine wafers can be implanted
  - Help determine if there is a change in histopathological grading
- 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
- Rechallenge with Temozolomide
- Re-Irradiation
  - EBRT
  - Stereotactic Radiosurgery
- **Clinical Trials**

Benefit of More Complete GBM Resection

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


OS=overall survival; RT=radiotherapy; 5-ALA=5-aminolevulinic acid–induced tumor fluorescence.
Current Surgical Standard of Care in GBM

There is a consensus that maximal safe resection is the goal for neurosurgeons when dealing with newly diagnosed GBM patients, even when full resection is not possible. This consensus is reflected in current guidelines:

- European Society Medical Oncology (EMSO) 2009
- National Comprehensive Cancer Network (NCCN) 2010
- American Association of Neurological Surgeons (AANS)/ Congress of Neurological Surgeons (CNS) Section on Tumors 2008
- National Cancer Institute (NCI), 2009
- National Institute for Health and Clinical Excellence (NICE) 2007
- German Cancer Society (DKG) 2010

Where’s the tumor?

White Matter

Cortical surface

white light illumination
Fluorescence-Guided Surgery (FGS)

- Improved intraoperative visualization
  - Real-time image guidance
- Permits more extensive resection of malignant brain tumors with infiltrative biology.
- Permits safer resection of malignant brain tumors in combination with intraoperative mapping for motor/language pathways.
- Impacts overall survival of patients with malignant brain tumors.

5-ALA Fluorescence-Guided Surgery

A. “white light”  
B. “blue light”

*TProvided by Dr. David Roberts of Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire.

5-ALA (Gliolan) Profile

- Heme Precursor – Aminolevulinic acid
- Accumulates and metabolized in malignant glioma cells
- Visualization only in blue light
  - Utilizing 510K-approved operative microscope systems
- Essentially nontoxic
  - Eye and skin phototoxicity within 24 h
  - Liver metabolism

PpIX Intraoperative Tumor Fluorescence and Real-Time Image-Guided Surgery

5-ALA Fluorescence-Guided Surgery (FGS)

Non-fluorescent, invisible  Strongly fluorescent

Stummer et al. 1998
Why Do Malignant Gliomas Fluoresce with 5-ALA?

• Several proposed mechanisms:
  • Decreased ferrochelatase activity permitting accumulation of PpIX.
  • Increased 5-ALA uptake by tumor cells
  • Disturbance in outflow of PpIX

PpIX Fluorescence and MRI
Gadolinium Enhancement

• Significant relationship between contrast enhancement on preop MRI and observable intraoperative PpIX fluorescence.
• Positive correlation between quantitative measurements of PpIX and gadolinium in glioma patients undergoing surgery.
• Residual fluorescence correlates with residual gadolinium contrast enhancement.

Roberts D. et al. J Neurosurg 2010
Clinical usefulness of 5-ALA

• Gliolan (5-ALA) is an effective intraoperative imaging agent
  – Used in real-time and does not interrupt surgery.
  – Obvious visual distinction between tumor and normal tissue
  – Provides information on the entire operative area visualized.
  – Easy to use (red-violet represents gross tumor)
    • Surgeon can use conventional methods to identify important motor and language pathways and better understand their anatomic relationship to any residual tumor
• Helps surgeon to achieve maximal tumor resection in a precise, safe, manner.
Does 5-ALA Image What It Purports to Image? (High grade glioma tissue?)

- Stummer et al. 1998 (Neurosurgery) and Stummer et al. 2000 (J Neurosurg):
  62 patients; 323 biopsies taken from borders of fluorescing tissue to correlate fluorescence with histopathology (data reanalyzed for threshold high density tumor)
  - Positive predictive value: 99.6%
  - Negative predictive value: 100%
  - Specificity: 99%
  - Sensitivity: 100%

- Phase II (ALS.28/GLI):
  Quantitative correlation of fluorescence intensity to histopathology.
  - 33 patients, 4 centers, 185 biopsies from transition zone
  - Positive predictive value of strong fluorescent tissue: 100.0%; 90% CI: 96.9% - 100.0%
  - Positive predictive value of weak fluorescent tissue in transition zone: 92.2%; 90% CI: 85.9% - 96.3%

Gliolan demonstrates unprecedented high positive and negative predictive value, specificity, and sensitivity for delineating tumor

<table>
<thead>
<tr>
<th>Study</th>
<th>PPV</th>
<th>NPV</th>
<th>Sensitivity</th>
<th>Specificity</th>
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<tbody>
<tr>
<td>MC-ALS28.GLI</td>
<td>96%</td>
<td>25%</td>
<td>68%</td>
<td>80%</td>
</tr>
<tr>
<td>Stummer 2000</td>
<td>99%</td>
<td>50%</td>
<td>90%</td>
<td>96%</td>
</tr>
<tr>
<td>Panciani 2012</td>
<td>89%</td>
<td>91%</td>
<td>91%</td>
<td>89%</td>
</tr>
<tr>
<td>Idoate 2011</td>
<td>98%</td>
<td>67%</td>
<td>89%</td>
<td>94%</td>
</tr>
<tr>
<td>Diez Valle</td>
<td>97%</td>
<td>92%</td>
<td>91%</td>
<td>97%</td>
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</table>

5-ALA induced fluorescence leads to
- a high rate of differentiating tumor and healthy tissue (PPV/NPV)
- a high rate in correctly identifying tumor and healthy tissue (sensitivity/ specificity)
5-ALA Fluorescence-Guided Surgery Does Lead To More Complete Resections

**% complete resection**

<table>
<thead>
<tr>
<th>Complete Resection (%)</th>
<th>PFS (based on MRI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>62.6 % ALA</td>
<td>p &lt; 0.0001</td>
</tr>
<tr>
<td>37.4 % WL</td>
<td></td>
</tr>
</tbody>
</table>

**PFS 6 months:**
- 35.2% vs. 21.8%
  
  (p=0.004, χ²)

**NB.** Stummer trial by and large did not include image guidance technology.

The majority of patients also did not undergo TMZ therapy.

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Increased Overall Survival with TMZ/XRT

**CLINICAL STUDY**

Prospective cohort study of radiotherapy with concomitant and adjuvant temozolomide chemotherapy for glioblastoma patients with no or minimal residual enhancing tumor load after surgery

- Walter Stummer · Thomas Meinl · Christian Eselt · Peter Martin · Olga Jakobs · Jörg Felsberg · Galina Rollenhager

- Received: 27 September 2011 / Accepted: 7 January 2012 / Published online: 4 February 2012

- 143 patients; median f/up 24 mos

- Median survival was 16.9 months for 107 patients with residual tumor diameters ≤ 1.5 cm (95%CI: 13.3-20.5), and 13.9 months (10.3-17.5) for 36 patients with residual tumor diameters > 1.5 cm and the univariate hazard ratio comparing partial vs. complete resection was 2.3.

- Pts with MGMT methylation and complete resection had the best prognosis
Winship Cancer Institute of Emory University

A Phase 2 Study of 5-Aminolevulinic Acid (ALA) to Enhance Visualization and Resection of Newly Diagnosed or Recurrent Malignant Gliomas (IND 112246)

PI: Costas G. Hadjipanayis, M.D, Ph.D.

Primary Endpoints: Safety and Extent of Resection
Correlative Study: Serum collection for exosome analysis
Extent of Resection: Shim, Holder and Cordova

Winship Phase II Gliolan Study

A Phase 2 Study of 5-Aminolevulinic Acid (ALA) to Enhance Visualization and Resection of Newly Diagnosed or Recurrent Malignant Gliomas

- Individuals with suspected newly diagnosed or recurrent malignant gliomas on MRI

- Fluorescence-guided microsurgical resection after 5-ALA (20 mg/kg) administration 3-5 h prior to surgery

- Confirmation of histopathology

- MRI within 48 h after surgery and every 3 months until tumor progression found in imaging

- Volumetric Imaging Review and Volumetric Residual Contrast Enhancement Analysis

NCI-CC
Winship Cancer Institute Phase II 5-ALA Gliolan Trial

- Have enrolled over 48 patients
  - 46 patients with malignant gliomas
  - 2 patients with brain mets
- 1 serious adverse event possibly associated with use of Gliolan
- Transient elevation of LFTs in patients
- Adverse events include a temporary skin rash and muscle weakness

5-ALA (Gliolan) Fluorescence-Guided Surgery
5-ALA EOR Analysis

<table>
<thead>
<tr>
<th>Control ID</th>
<th>Preoperative tumor volume (cm³)</th>
<th>Residual contrast-enhancing tumor volume (cm³)</th>
<th>EOR (%)</th>
<th>EOR Orthog (%)</th>
<th>Study ID</th>
<th>Preoperative tumor volume (cm³)</th>
<th>Residual contrast-enhancing tumor volume (cm³)</th>
<th>EOR (%)</th>
<th>EOR Orthog (%)</th>
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<tr>
<td>Ctrl01</td>
<td>13.74</td>
<td>1.79</td>
<td>12.03</td>
<td>n/m</td>
<td>ALA004</td>
<td>3.59</td>
<td>0.391</td>
<td>9.77</td>
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<tr>
<td>Ctrl02</td>
<td>50.33</td>
<td>8.80</td>
<td>37.49</td>
<td>n/m</td>
<td>ALA005</td>
<td>83.884</td>
<td>1.787</td>
<td>2.72</td>
<td>n/m</td>
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<tr>
<td>Ctrl03</td>
<td>10.86</td>
<td>1.18</td>
<td>9.94</td>
<td>5.13</td>
<td>ALA007</td>
<td>22.36</td>
<td>2.225</td>
<td>9.95</td>
<td>3.55</td>
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<td>Ctrl04</td>
<td>19.38</td>
<td>3.53</td>
<td>16.85</td>
<td>0</td>
<td>ALA008</td>
<td>41.81</td>
<td>2.728</td>
<td>6.52</td>
<td>0</td>
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<td>Ctrl05</td>
<td>30.21</td>
<td>2.48</td>
<td>8.22</td>
<td>1.66</td>
<td>ALA009</td>
<td>8.38</td>
<td>0.744</td>
<td>8.87</td>
<td>7.52</td>
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<td>Ctrl06</td>
<td>34.44</td>
<td>11.06</td>
<td>23.18</td>
<td>78.3</td>
<td>ALA10</td>
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<td>6.128</td>
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<td>0.70</td>
<td>0</td>
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<td>15.956</td>
<td>0.995</td>
<td>6.23</td>
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<td>Ctrl11</td>
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<td>7.84</td>
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<td>4.806</td>
<td>0.413</td>
<td>8.59</td>
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<td>Ctrl12</td>
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<td>6.911</td>
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<td>n/m</td>
<td>ALA21</td>
<td>66.757</td>
<td>5.859</td>
<td>8.77</td>
<td>n/m</td>
</tr>
</tbody>
</table>

Mean percent residual tumor for control cohort 89.31 ± 7.45 %

Mean percent residual tumor for experimental cohort 95.15 ± 3.98 %

Significantly different at p<0.01 using the nonparametric Wilcoxon Rank-Sum Test

Conclusions I

- 5-ALA induced fluorescence leads to a:
  - high rate of differentiating tumor and healthy tissue (PPV/NPV)
  - high rate in correctly identifying tumor and healthy tissue (sensitivity/specifity)
- 5-ALA (Gliolan) has been shown to improve the extent of GBM resection with a favorable safety profile.
- In the process of seeking FDA approval with pre-NDA.
- Expanding Winship Phase II study to 3 other centers (U Mich, Wash U, Henry Ford).
- Phase III study in preparation.
TARGETED GBM THERAPY.....

The Cancer Genome Atlas Research Network and GBM

-DNA copy number, gene expression and DNA methylation aberrations in 206 glioblastomas

Nature 2008
WE KNOW THAT:

- Most GBM tumors recur at the site of their initial treatment due to surrounding cancers cells resistant to therapy.
- Glioblastoma stem cells (GSCs) are known to be integral to tumor development, perpetuation, and therapy resistance.
- Epidermal growth factor receptor (EGFR) represents the most common GBM alteration with overexpression on cells.
Magnetic Nanoparticles for Malignant Brain Tumor Imaging and Therapy

- Nanoscale multifunctional agents that provide simultaneous imaging and therapeutic efficacy
- MRI contrast agent
- Tumor targeting and therapy with monoclonal antibodies, drug delivery, siRNA, and/or local hyperthermia
- Biocompatible


A New Approach For GBM Targeting

- Conjugate GBM-specific antibody (EGFRvIIIAb) to magnetic iron-oxide nanoparticles (EGFRvIIIAb-IONPs)
  - Amphiphilic triblock copolymer coated
- MRI contrast enhancement of GBM cells
- Antitumor apoptotic effect and lower EGFR phosphorylation
- Nontoxic to nl cells in the brain
- Able to distribute well in the rodent brain by CED and disperse days later and increase OS

Hadjipanayis CG et al. Cancer Res 2010
**Targeting of Patient-Derived GBM Neurospheres and Apoptosis Induction by EGFRvIIIAb-IONPs**

**EGFRvIIIAb-IONPs promote apoptosis in glioma stem cell-containing neurospheres.** Neurospheres from Patient # 30 and 74 were treated with IONPs, EGFRvIIIAb-IONPs, IgG, and EGFRvIIIAb. Western blot analysis revealed elevated levels of cleaved caspase-3 after treatment with the EGFRvIIIAb-IONPs. Neurospheres from Patient #30, which express EGFRvIII and the GSC marker CD133, have higher levels of apoptosis induction.

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**No Human Astrocyte Toxicity**

![Graph showing no human astrocyte toxicity](image-url)
Apoptosis by TRAIL Conjugated Magnetic Nanoparticles

- TRAIL conjugated to ferric oxide NP
- Increased apoptosis in GBM cells and glioma stem cells (GSCs) as compared to free TRAIL
- Significant antitumor effect in vivo

Cetuximab-IONPs

- Cetuximab is a chimeric monoclonal Ab that cross reacts with both the wt EGFR and EGFRvIII
  - FDA approved for colon and head and neck cancers
- Majority of GBM tumors overexpress wt EGFR
- Taken to clinical trials for GBM in the past
- Cetuximab-IONPs can therapeutically target EGFR-expressing GBM cells including glioma stem cells (GSCs) in vitro and in vivo.
Canine Model of Convection-Enhanced Delivery of Cetuximab-Conjugated Iron-Oxide Nanoparticles Monitored With Magnetic Resonance Imaging

Simon Platt, BVM&S, MRCVS, Edjash Nduom, MD, Marc Kent, DVM, Courtenay Freeman, DVM, Revaz Machaidze, BS, Milota Kuzsova, PhD, Liya Wang, MD, Hui Mao, PhD, and Costas G. Hadjipanayis, MD, PhD


Spontaneous Canine Glioma Trial-
University of Georgia
S. Platt and C. Hadjipanayis

Cetuximab conjugated iron-oxide nanoparticles
(cetuximab-IONPs)

Funding by American Kennel Foundation
Fig.  First canine EGFR-expressing spontaneous glioma patient treated with cetuximab-IONPs by CED. MRIs with gadolinium (gad) and T2WI were obtained preop, 24 h and 7 d after partial tumor resection.

Fig. CED setup in the first spontaneous canine glioma patient. Two catheters were placed in the residual tumor and the canine underwent a 3 d CED infusion (0.5 μl/min) of cetuximab-IONPs (0.5 mg/ml). Catheters were tunneled subcutaneously (A) and connected to separate pumps (B) secured on the dorsal surface of the head (C). D, MRI showing intratumoral positioning of CED catheter and initial distribution of cetuximab-IONPs within 24 h after CED.
Conclusions II

• IONPs represent a multifunctional clinical tool sensitive to MR imaging that can be designed to therapeutically target GBM.
• Cetuximab-IONPs represent a potential therapeutic that can target patient derived EGFR-expressing GBM cells including GSCs.
• Antitumor efficacy is found in rodents with orthotopic human EGFR-expressing GBM xenografts after CED.
• Feasibility, safety, and efficacy is found in canines with EGFR-expressing spontaneous gliomas
• Cetuximab-IONP CED may serve as the basis for a human clinical trial.

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 will also play an important role in GBM management.
Funding

- NIH K08 Award
- NIH NCI P50 Pilot Project Grant
- NIH R01 (Brat and Hadjipanayis)
- NIH R21 (Shim, Holder, and Hadjipanayis)
- Georgia Cancer Coalition
- Southeastern Brain Tumor Foundation
- Dana Foundation
- Robbins Scholar Award
- American Kennel Club (Platt and Hadjipanayis)

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University of Georgia Veterinary School of Medicine

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