Current and Future Treatment Options for Glioblastoma

Santosh Kesari, MD, PhD, FANA, FAAN

Chair, Department of Translational Neurosciences and Neurotherapeutics
John Wayne Cancer Institute & Pacific Neuroscience Institute
Director of Neuro-Oncology, Providence Saint John’s Health Center
John Wayne Cancer Institute and Pacific Neuroscience Institute
Providence Saint John’s Health Center
What I have learned in past ~20yrs

Collaborate
• Team sport/effort
• Scientists, clinicians (surgery, oncology, radiation, etc)
• Patients

Innovate
• No new drug developed for brain cancer in >20yrs
• Make new drugs

Accelerate
• Incorporate latest knowledge
• Do studies faster- “Research in Action”

Motivated and Driven by Dedicated Supporters and Philanthropy

Hippocrates: “The art is long, life is short”
Neuro-Oncology: A Distinct Specialty
A Unique Opportunity

- Increasing disease due to aging population and longer survival of cancer patients who develop neurological complications
  - Primary brain tumors
  - Metastatic brain tumors
  - Leptomeningeal metastasis
  - Seizures
  - Cognitive dysfunction, mood disorders
  - Fatigue
  - Myopathy
  - Endocrine dysfunction
  - Bone fractures
  - Headache and cancer pain
  - Hydrocephalus
  - Neurotoxicity
  - Neuropathy
  - Regenerative medicine/stem cells
  - And more....

- Orphan diseases
- Need a organized, multidisciplinary, team-based approaches to accelerate cures
## Brain Cancer Incidence – 2016

<table>
<thead>
<tr>
<th>Site</th>
<th>New Cases</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>180,890</td>
<td>26,120</td>
</tr>
<tr>
<td>Breast</td>
<td>249,260</td>
<td>40,890</td>
</tr>
<tr>
<td>Lung</td>
<td>224,390</td>
<td>158,080</td>
</tr>
<tr>
<td>Colon</td>
<td>95,270</td>
<td>49,190</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>81,080</td>
<td>21,270</td>
</tr>
<tr>
<td>Skin-melanoma</td>
<td>76,380</td>
<td>10,130</td>
</tr>
<tr>
<td>Kidney</td>
<td>62,700</td>
<td>14,240</td>
</tr>
<tr>
<td><strong>Nervous system</strong></td>
<td><strong>23,770</strong></td>
<td><strong>16,050</strong></td>
</tr>
<tr>
<td>Cervix</td>
<td>12,990</td>
<td>4,120</td>
</tr>
<tr>
<td>Testis</td>
<td>8,720</td>
<td>380</td>
</tr>
</tbody>
</table>

Incidence Increases with Age - 2015

[Graph showing age-adjusted incidence rates per 100,000 for different types of brain tumors across various age groups (20-44, 45-54, 55-64, 65-74, 75+ years). The graph includes different types of tumors such as All Other Astrocytoma, Oligoastrocytic Tumors, Glioblastoma, Oligodendroglioma, Vestibular schwannoma, Tumors of the Pituitary, and Meningioma (non-malignant).]
Primary Brain Tumors - 2015

Gliomas account for 27% of all tumors
80% of malignant tumors
Maximal surgical resection

Involved-field RT +

Concurrent temozolomide 75 mg/m²

6-12 cycles of temozolomide
150-200 mg/m²

*2005: Temodar: 1st new drug for brain tumor in decades

“Recent” Progress: New Standard of Care for Glioblastoma

- Median survival 14.6 vs. 12.1 months
- 2-year survival 26.5% vs. 10.4%
Biomarkers of Response in Glioblastoma

Figure 2. Kaplan–Meier Estimates of Overall Survival, According to MGMT Promoter Methylation Status.
Development of Targeted Therapeutics

- CML: 1 gene mutation
  - 1 targeted drug
- Many other drugs developed for other pathways
- Many tested in gliomas over the last decade

But for most part initial trials of targeted therapeutics in gliomas have been unsuccessful
Adult Brain Tumor: Targeted Therapeutics Responders

*2009: Avastin 2nd new drug for brain tumor
Pediatric Brain Tumors:
Everolimus for Subependymal Giant Cell Astrocytomas

*2012: Affinitor: 3rd new drug for brain tumors
Integrated Genomic Analysis Identifies Clinically Relevant Subtypes of Glioblastoma Characterized by Abnormalities in PDGFRA, IDH1, EGFR, and NF1
Complex Network of Glioma Gene Interactions

- 7 landscape genes significantly associated with survival
- Ch 7
  - POLD2-DNA polymerase delta 2 small subunit,
  - CYCS- cytochrome C, somatic
- Ch 8
  - MYC
- Ch 10
  - AKR1C3-Aldo-keto reductase family 1 member C3
  - YME1L1- YME1-like 1
  - ANXA7-annexin A7
  - PDCD4-programmed cell death 4
Bevacizumab (Avastin®)

How Avastin Starves a Tumor

Tumors need blood, and they have a devious way to get it:

>>> They secrete a protein called VEGF that docks with receptors in nearby blood vessels, stimulating the growth of new blood vessels.

>>> Genentech foils this plot with Avastin, a drug that binds with VEGF and prevents that protein from attaching to receptors. New blood vessels don’t form, and the tumor starves.
VEGF Inhibitors: Radiographic Response

- ~30% respond durably
- What is the biomarker?
- Looking at genomics and expression profiles of responders vs. non-responders to find a biomarker.
Bevacizumab for recurrent malignant gliomas
Efficacy, toxicity, and patterns of recurrence

Figure 1 Distant recurrence in a patient with recurrent malignant glioma treated with bevacizumab and irinotecan

Figure 2 Local recurrence in a patient with recurrent malignant glioma treated with bevacizumab and irinotecan

Figure 3 Diffuse recurrence in a patient with recurrent malignant glioma treated with bevacizumab and irinotecan
Why have we not made faster progress?

Barriers

• Tumor/Disease heterogeneity
• Blood-brain barrier
• Immunosuppressive microenvironment
• Steriod use
• Radiation/Chemotherapy
• Tumors are different genetically
• Limits drug access
• Immune system inhibited
• Immune system inhibited
• Immune system inhibited/
  Promotes aggressive recurrence

Better Drugs are Needed!
Bedside to Bench Approach

- Individual off-label responders
- Lead to Lab based research studies
- Lead to Investigator-initiated clinical trials

Leukemia drug- Imatinib (Gleevec)

Baseline

1mth later

Off-label use
Bedside to Bench Approach

Differential sensitivity to PDGFRA inhibitors correlates with PDGFRA expression

Supported by the Kenney/Quinn/Ford Brain Tumor Research Foundation of the Boston Fire Department

- Individual off-label responders
- Lead to Lab based research studies
- Lead to Investigator-initiated clinical trials
Clinical Trial: 1st Precision Medicine Trail in Glioblastoma

Molecular Profiling showed PDGFR activation

January 2014

Started clinical trial of Tasigna (nilotinib)

August 2016

• Individual off-label responders
• Lead to Lab based research studies
• Lead to Investigator-initiated clinical trials
Treatment of Medulloblastoma with Hedgehog Pathway Inhibitor GDC-0449

Charles M. Rudin, M.D., Ph.D., Christine L. Hann, M.D., Ph.D., John Laterra, M.D., Ph.D., Robert L. Yau, Ph.D., Christopher A. Callahan, M.D., Ph.D., Ling Fu, M.D., Thomas Holcomb, M.S., Jeremy Stinson, B.S., Stephen E. Gould, Ph.D., Barbara Coleman, R.N., C.C.R.P., Patricia M. LoRusso, D.O., Daniel D. von Hoff, M.D., Frederic J. de Sauvage, Ph.D., and Jennifer A. Low, M.D., Ph.D.

Figure 1. Tumor Response on Positron-Emission Tomographic (PET) Scanning. Whole-body projections from $^{18}$F-fluorodeoxyglucose (FDG)–PET scans are shown; Panel A, the baseline scan; Panel B, the repeat scan after 2 months of therapy with the hedgehog pathway inhibitor; Panel C, the repeat scan after 3 months of therapy.
SHH Inhibitors in Pediatric Brain Tumors

TREATMENT OF MEDULLOBLASTOMA WITH HEDGEHOG PATHWAY INHIBITOR GDC-0449

Charles M. Rudin, M.D., Ph.D., Christine L. Hann, M.D., Ph.D.,
John Laterra, M.D., Ph.D., Robert L. Yauch, Ph.D.,
Christopher A. Callahan, M.D., Ph.D., Ling Fu, M.D., Thomas Holcomb, M.S.,
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Figure 1. Tumor Response on Positron-Emission Tomographic (PET) Scanning.
Whole-body projections from 18F-Fluorodeoxyglucose (FDG)–PET scans are shown. Panel A shows the pretreatment scan; Panel B, the repeat scan after 2 months of therapy with the hedgehog pathway inhibitor GDC-0449; and Panel C, the repeat scan after 3 months of therapy.

Figure 2. Tumor-Specific Hedgehog Pathway Activation.
Panel A shows the expression of GLI family zinc finger 1 (GLI1) and patched homologue 1 (PTCH1) messenger RNA in the patient’s tumor (red dot) relative to the expression in a panel of 55 banked medulloblastoma samples (gray dots). GLI1 and PTCH1 expression levels were assessed with the use of real-time polymerase-chain-reaction assays, and results are presented as normalized gene expression (2−ΔΔCt). Panel B shows the nucleotide sequence of the PTCH1 gene in specimens of the patient’s skin and tumor. In the tumor specimen, both forward and reverse reactions show a homozygous mutation at position 2720, resulting in a G→C change (arrow).
Tumor Heterogeneity: Mixed responses

Recurrence

Post-CT-322

Post-Avastin
Precision medicine Adapt as the Tumors Evolve:
Case 1: 42 yo RHM uMGMT GBM

At start of Treatment

Progressed on Temodar

1st Profiling: mTOR, EGFR mutation

XRT/TMZ

Surgery

Affinitor Tarceva
Precision Medicine Pathway:

NextGen GBM Signature Biomarker-Driven Trials

Newly-diagnosed GBM

BIOMARKER
- EGFR
- PDGFR
- MET
- mTOR
- Immune Markers

THERAPY
- Erlotinib
- Imatinib
- Tivatinib
- Everolimus
- Immunotherapy

Treat patients individually based on their own unique characteristics

Collaboration with physicians, scientists, patients, research institutions, industry and Philanthropy
Why have we not made faster progress?

Barriers

- Tumor heterogeneity
- **Blood-brain barrier**
- Immunosuppressive microenvironment
- Steriods use
- Radiation/Chemotherapy

- Tumors are different genetically
- **Limits drug access**
- Immune system inhibited
- Immune system inhibited
- Immune system inhibited/
  Promotes aggressive recurrence
Does Enough Drug Get into the Brain?

Response and Resistance in a Non–Small-Cell Lung Cancer Patient With an Epidermal Growth Factor Receptor Mutation and Leptomeningeal Metastases Treated With High-Dose Gefitinib

Table 1. Relationship Between Gefitinib Dose, Gefitinib Concentration, CSF Cytology, and Transaminases

<table>
<thead>
<tr>
<th>Date</th>
<th>Gefitinib Dose (mg)</th>
<th>CSF Site</th>
<th>Gefitinib Concentration, CSF (nM)</th>
<th>CSF Cytology Result</th>
<th>ALT/AST (mg/dL)</th>
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</thead>
<tbody>
<tr>
<td>September 5, 2004</td>
<td>500</td>
<td>LP</td>
<td>6.2</td>
<td>–</td>
<td>19/15</td>
</tr>
<tr>
<td>September 21, 2004</td>
<td>500</td>
<td>LP</td>
<td>18*</td>
<td>+</td>
<td>19/15</td>
</tr>
<tr>
<td>October 13, 2004</td>
<td>750</td>
<td>LP</td>
<td>32</td>
<td>+</td>
<td>30/20</td>
</tr>
<tr>
<td>November 23, 2004</td>
<td>750</td>
<td>Ommaya</td>
<td>NA</td>
<td>+</td>
<td>22/20</td>
</tr>
<tr>
<td>December 15, 2004</td>
<td>1,000</td>
<td>Ommaya</td>
<td>NA</td>
<td>–</td>
<td>91/57</td>
</tr>
<tr>
<td>January 7, 2005</td>
<td>1,000</td>
<td>Ommaya</td>
<td>42</td>
<td>–</td>
<td>122/47</td>
</tr>
<tr>
<td>February 16, 2005</td>
<td>1,250</td>
<td>Ommaya</td>
<td>39</td>
<td>NA</td>
<td>43/35</td>
</tr>
</tbody>
</table>

Abbreviations: LP, lumbar puncture; NA, not available.

*On September 9, 2004, the patient’s treatment was changed from phenytoin (an enzyme-inducing antiepileptic drug) to levetiracetam (a nonenzyme-inducing antiepileptic drug).

- CSF is a window into the brain
- All Ph 1 clinical trials include CSF drug levels and biomarkers
2 weeks after high dose Methotrexate
Innovative Drugs:

- **ANG1005** – drug complex targeting BBB transport
  - Started clinical trial of **ANG005**
  - Reformulation of old breast cancer drug Taxol

September 2014

February 2015

Renewed focus on innovative development of drugs that cross BBB
G202: targeting toxins to tumor vessels

Brain: PSMA-

GBM: PSMA+
Innovative Devices: Novocure

Tumor Treating Fields – An entirely novel modality for antimitotic therapy

Overcomes BBB

- FDA approved Nov 2015
- Published in JAMA Dec 2015
Innovative Technologies: Novocure
Optune Device: Tumor Treating Electrical Fields

Interim analysis of the EF-14 trial: A prospective, multicenter trial of NovoTTF-100A together with temozolomide compared to temozolomide alone in newly diagnosed glioblastoma

Late breaking abstract. Society of Neuro-Oncology Annual Meeting, Miami Beach, 15. November 2014

Roger Stupp, Eric T Wong, Charles B Scott, Sophie Taillibert, Andrew Kanner, Santosh Kesari, and Zvi Ram
on behalf of the EF-14 investigators

Contact: roger.stupp@usz.ch
Innovations: Novocure and Nativis

- Other devices in trials now...Nativis
- Bioelectronics and wearable sensors are in development
Background: Why have we not made faster progress?

Barriers

- Tumor/Disease heterogeneity
- Blood-brain barrier
- Immunosuppressive microenvironment
- Steroid use
- Radiation/Chemotherapy
- Tumors are different genetically
- Limits drug access
- Immune system inhibited
- Immune system inhibited
- Immune system inhibited/Promotes aggressive recurrence
Progress in Immuno-Oncology

- Antibodies
  - VEGF
  - EGFR
  - PDGFR
- Vaccines
  - Peptide/Protein/Tumor cell lysates
  - Viral
  - Dendritic Cell
  - Oncolytics
- Small molecule agonists and inhibitors
  - IDO
  - TGF-beta
- Cytokines
  - IL-2
- Immune checkpoint modulation
  - CTLA-4
  - PD-1, PD-L1
  - TNFSRF
- Cellular therapy
  - CARs, TCRs

Brain Cancers

- We have tried them all
- Need complete removal
- Steriods limiting
- Toxicity limiting with newer agents

Suppressive mechanisms

- MDSC cell
  - Secretion of NO, arginine, and ROS
  - Sequestration of cysteine
  - Impaired differentiation
  - Defective antigen presentation
- Treg cell
  - Secretion of suppressive cytokines (TGF-β, IL-10)
  - Sink for IL-2, IL-7, IL-12, and IL-15
  - Impaired activation of CTLs
- Macrophage
  - M2 differentiation/cytokine profile
  - Defective antigen presentation
  - Lack of costimulation for T cells
  - Impaired tumoricidal activity
- Dendritic cell
  - IDO expression; induction of Tregs
  - Impaired maturation
  - Defective antigen presentation
  - Lack of costimulation for T cells
- Cancer cell
  - Loss of MHC class I and antigen processing machinery
  - Antigen loss variants
  - Secretion of VEGF, GM-CSF, G-CSF, and gangliosides

Cancer Research Reviews

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Immunotherapy Responses in Brain Cancer: PCNSL

- 70 yo fireman with PCNSL that relapsed following kitchen sink including chemotherapy, transplant and radiation.
- Started Nivolumab
Precision Immunotherapy:
NextGen GBM Signature Biomarker-Driven Trials

Newly-diagnosed GBM

BIOMARKER
- Marker #1
- Marker #2
- Marker #3
- Marker #4
- Immune Markers

THERAPY
- ImmuneRx #1
- ImmuneRx #2
- ImmuneRx #3
- ImmuneRx #4
- Immunotherapy

Treat patients individually based on their own unique immune characteristics