GLIOMA OVERVIEW

➤ INFILTRATIVE, MALIGNANT, PRIMARY BRAIN TUMOR

➤ Not resectable
➤ Not curable
➤ CNS-born
➤ Rarely metastasize

GLIOMAS

➤ WHO 2016 GLIOMA CLASSIFICATION

- IDH 1/2 Wild Type (WT): Infiltrative Astrocytoma
- IDH 1/2 Mutant: IDH-Mutant, Secondaries (WHO II/III)
- IDH-WT, Secondary Glioblastoma (WHO IV)
- IDH-WT, Secondary Glioblastoma (WHO IV)
- Primary Glioblastoma (WHO IV)
**Glioma Imaging**

- MRI FINDINGS – WHO Grade II-III Gliomas
- MRI FINDINGS – WHO Grade IV Glioblastomas

**Glioma Prognosis**

- Prognosis better for Oligodendrogliomas
  - Explained by 1p/19q co-deletion

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1. MRI FINDINGS – WHO Grade II-III Gliomas
2. MRI FINDINGS – WHO Grade IV Glioblastomas
3. Prognosis better for Oligodendrogliomas
4. Explained by 1p/19q co-deletion
Mutations in Isocitrate Dehydrogenases linked to Gliomagenesis

Prognosis predicted by mutations in IDH1 (and IDH2)

IDH1/2 Mutant, Secondary Glioblastoma
IDH-WT, Secondary Glioblastoma
Primary Glioblastoma

BRAF mutation/fusion
PA and PXA

Worse Prognosis

WORSE PROGNOSIS WHO Grade

WHO 2016 GLIOMA CLASSIFICATION

Molecular Profile

Gliomas

WHO 2016 GLIOMA CLASSIFICATION
Infiltrative Glioma
IDH1/2 Mutant
Infiltrative Glioma
IDH 1/2 Wild Type (WT)
Infiltrative Astrocytoma
IDH-WT Astrocytoma
"Pre-Glioblastoma" (WHO II-III)
IDH-WT, Secondary Glioblastoma
Primary Glioblastoma (WHO IV)

gliomas ➤ TREATMENT: IDH-WT WHO Grade III-IV Astrocytomas
➤ Surgery + radiation + concurrent/adjuvant temozolomide

gliomas ➤ TREATMENT: Glioblastomas
➤ Surgery + radiation + concurrent/adjuvant temozolomide

Stupp R, NEJM 2005

gliomas ➤ TREATMENT: Glioblastomas
➤ MGMT promoter methylation status predicts response
➤ O6-methylguanine methyltransferase (MGMT) – DNA repair gene
➤ MGMT promoter hypermethylation leads to gene silencing
➤ Predicts response to alkylating chemotherapy, like temozolomide and nitrosoureas
➤ Predicts response to oxidizing radiation

Hegi ME, NEJM 2005
TREATMENT: Glioblastomas

- Tumor Treating Fields (TTF) at recurrence (2010) and upfront (2016)

Survival Benefit extends to 4 and 5-year

- Surgery + radiation + concurrent/adjuvant temozolomide + TTF

Survival Benefit increased by 3-5 months

2-Year Survival rates increased by ~15%

Low Compliance

Stupp R, JAMA 2016

TREATMENT: Glioblastomas

- Surgery + radiation + concurrent/adjuvant temozolomide + TTF

Median OS increased by 3-5 months

2-Year Survival rates increased by ~15%

Stupp R, JAMA 2016
Infiltrative Glioma

IDH1/2 Mutant

IDH 1/2 Wild Type (WT)

Infiltrative Glioma

Infiltrative Astrocytoma

IDH-WT Astrocytoma

“Pre-Glioblastoma” (WHO II-III)

IDH-WT, Secondary Glioblastoma (WHO IV)

Primary Glioblastoma (WHO IV)

TREATMENT: Extrapolated to WHO II-III, IDH-WT Astrocytomas

Surgery + radiation + concurrent/adjuvant temozolomide + TTF(?)

TREATMENT: Extrapolated to WHO II-III, IDH-WT Astrocytomas

TTF trials pending for WHO III

Patient compliance and physician acceptance remain low

Unclear benefit in WHO II

Unclear benefit in elderly and/or poor functional status

Hypofractionated (shortened) radiation course

Temozolomide alone for MGMT hypermethylated tumors

TREATMENT: Implications of Molecular Profile

IDH1/2 Mutant astrocytomas

ATRX loss, p53 mutation

IDH-Mutant, Secondary Glioblastoma

Primary Glioblastoma

TREATMENT: IDH-mutant Gliomas
Infiltrative Glioma

IDH1/2 Mutant

Infiltrative Glioma

1p/19q Co-Deletion:
Oligodendroglioma
(WHO II-III)

ATRX loss, p53 mutation

Astrocytoma
(WHO II-III)

IDH-Mutant,
Secondary Glioblastoma
(WHO IV)

IDH 1/2 Wild Type (WT)

Infiltrative Astrocytoma

Pre-Glioblastoma

IDH-Mutant,
Secondary Glioblastoma
(WHO IV)

Primary Glioblastoma
(WHO IV)

➤ TREATMENT: IDH-mutant, 1p/19q co-deleted Oligodendrogliomas

➤ TREATMENT: IDH-mutant, 1p/19q co-deleted Oligodendrogliomas

➤ Surgery + Radiation + Procarbazine, CCNU, Vincristine (PCV)

➤ TREATMENT: IDH-mutant, 1p/19q co-deleted Oligodendrogliomas

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**Gliomas**

- **TREATMENT: IDH-mutant, 1p/19q co-deleted Oligodendrogliomas**
  - Procarbazine, CCNU, Vincristine (PCV)
  - WHO grade III
    - Surgery + PCV + radiation
  - WHO grade II
    - Observe:
      - **LOW RISK** (<40 years, unilateral, & gross total resection)
      - PCV + radiation:
      - **HIGH RISK** (>40 years, bilateral, or subtotal resection)

- **TREATMENT: IDH-mutant, 1p/19q co-deleted Oligodendrogliomas**
  - PCV superior to temozolomide, but more toxic

<table>
<thead>
<tr>
<th>TOXICITY vs. CONTROL</th>
<th>PCV</th>
<th>TEMOZOLMIDE</th>
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<tbody>
<tr>
<td>Toxicity</td>
<td>10-40%</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>Noncompliance/Refusal</td>
<td>5-10%</td>
<td>&lt;5%</td>
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<tr>
<td>Response Rate</td>
<td>90-100%</td>
<td>35-80%</td>
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<tr>
<td>Median Time to Progression</td>
<td>7.2 years</td>
<td>3.2 years</td>
</tr>
<tr>
<td>Median Overall Survival</td>
<td>10.5 years</td>
<td>7.6 years</td>
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</tbody>
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- **Balancing Treatment Toxicity vs. Disease Control**
- **PCV vs. TMZ?**
- Radiation upfront or deferred to recurrence?
  - Radiation-induced cognitive deficits

**Infiltrative Glioma**

IDH1/2 Mutant

- ATRX loss, p53 mutation

**Infiltrative Astrocytoma**

IDH-Mutant, Secondary Glioblastoma

**Glioblastoma**

IDH 1/2 Wild Type (WT)

**Pre-Glioblastoma**

Miami Cancer Institute

BAPTIST HEALTH SOUTH FLORIDA
TREATMENT: IDH-mutant Astrocytomas
- Surgery + radiation + concurrent/adjuvant temozolomide?
- Surgery + PCV + radiation?

Additive benefit of molecular profiles
- 1p/19q co-deletion > IDH1 mutations > MGMT hypermethylation
- Toxicity vs. Control
- Timing

Chemotherapy alone for WHO grade II?

TREATMENT: Multimodal Approach

Cutting-Edge, Evidence-Based Therapy
- Chemotherapy
- Radiation
- Tumor Treating Fields
- Biologics
- Immunotherapy
- Surgery
TREATMENT: Multimodal Approach

- Chemotherapy
- Radiation
- Surgery
- Immunotherapy
- Genomics & Molecular Profiling

TREATMENT: Biologics

- Bevacizumab (VGEF) inhibits angiogenesis
  - Initial promising results:
    - Progression-free but not overall survival benefit
    - Dramatic MRI response due to steroid-like effect
    - Increasing concern for more invasive phenotype after exposure
  - Palliative benefit only

TREATMENT: Biologics

- EGFR amplification and/or EGFRvIII mutation
  - EGFR inhibitors poor CNS penetrance
➤ TREATMENT: Biologics
➤ EGFR amplification and/or EGFRvIII mutation
➤ EGFR inhibitors poor CNS penetration ➔ pulse dosing?

➤ Rindopepimut vaccine targeted EGFRvIII ➔ negative!

➤ ABT414 antibody drug conjugate (ADC)
➤ Anti-EGFR antibody + cytotoxic Monomethyl Auristatin F or MMAF
Cutting-Edge, Evidence-Based Therapy

TREATMENT: Biologics
- EGFR amplification and/or EGFRvIII mutation
  - EGFR inhibitors poor CNS penetration ➔ pulse dosing?
- Rindocepimut vaccine targeted EGFRvIII ➔ negative!
- ABT414 antibody drug conjugate (ADC)
  - Anti-EGFR antibody + cytotoxic Monomethyl Auristatin F or MMAF
  - Promising early response, now in Phase III trial

TREATMENT: Biologics for rare glioma subtypes
- BRAF-V600E and possibly BRAF fusion alterations in PXA or PA
  - Regimen based on BRAF-V600E mutant melanoma
  - BRAF inhibitor with/without concurrent MEK inhibitors
    - Initial promising results, ongoing trials
- H3-K27M Diffuse Malignant Glioma
  - Limited options, prognosis remains poor
  - Ongoing trials targeting mutation and downstream effects

TREATMENT: Immunotherapy

TREATMENT
GLIOMAS

➤ TREATMENT: Immunotherapy
➤ Vaccines – Negative or In Development
➤ CTLA-4 Inhibitors in development
  ► Ipilimumab – combination therapy, reduced dose
➤ Checkpoint Inhibitors

➤ Checkpoint Inhibitors
  ► Nivolumab and Pembrolizumab in trials for gliomas
GLIOMAS

➤ TREATMENT: Immunotherapy
  ➤ Vaccines – Negative or In Development
  ➤ CTLA-4 Inhibitors
  ➤ Checkpoint Inhibitors
  ➤ Response linked to high mutational load

TREATMENT: Multimodal

Chemotherapy
Tumor Treating Fields
Biologics
Immunotherapy
Surgery
Radiation

➤ TREATMENT: Evolving
  ➤ Guided by Genomic and Molecular Profiles
  ➤ Advanced by Clinical Trials
  ➤ Highly Variable and Unpredictable Course

Gliomas - Summary

➤ TREATMENT: Personalized

Genomics & Molecular Targets

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QUESTIONS?

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