Malignant/High Grade Tumors: Update in Treatment and Care

Sean Grimm, MD and Vinai Gondi, MD
Co-Directors, Brain & Spine Tumor Center,
Northwestern Medicine Cancer Center Warrenville

Malignant/High Grade Tumors: Update in Treatment and Care
Incidence Distribution of All Intracranial Tumors by Histology

- Meningioma: 30.1%
- Glioblastoma: 20.3%
- Pituitary: 6.3%
- Ependymomas: 9.8%
- Embryonal, including medulloblastoma: 1.7%
- Nerve Sheath: 8.0%
- Lymphoma: 3.1%
- Oligodendrogliomas: 3.7%
- Craniopharyngioma: 0.7%
- Astrocytomas: 9.8%
- All Other: 13.9%
Malignant (high grade) primary brain tumors

- **Glioma**
  - Anaplastic oligodendroglioma (WHO Grade III)
  - Anaplastic astrocytoma (WHO Grade III)
  - Anaplastic ependymoma (WHO grade III)
  - Glioblastoma (WHO Grade IV)

- **Lymphoma**

- **Embryonal**
  - Medulloblastoma (WHO Grade IV)
Malignant/High grade glioma 2015

- Anaplastic oligodendroglioma
- Anaplastic astrocytoma
- Mixed oligoastrocytoma
- Glioblastoma
Future classification scheme

• Better understanding of the genetic and molecular biology of the disease
• Biologically-based classification schema
• Biomarkers guide prognosis and therapy
• Can separate into three groups based on 1p/19q co-deletion and Isocitrate dehydrogenase (IDH) mutation
  • Type 1: 1p/19q co-deletion and IDH mutation
    – Classical oligodendroglioma and anaplastic oligodendroglioma
  • Type 2: 1p/19q intact and IDH mutation
  • Type 3: Absence of IDH mutation
    – Clinically behaves like primary glioblastoma
    – Have genetic abnormalities common in glioblastoma
Anaplastic glioma – Initial treatment

• Anaplastic oligodendroglioma - Type 1 (1p/19q co-deletion and IDH mutation)
  – Radiotherapy followed by PCV chemotherapy
  – Radiotherapy with concurrent TMZ followed by TMZ chemotherapy

• Anaplastic oligoastrocytoma and Anaplastic astrocytoma - Type 2 (1p/19q intact and IDH mutation)
  – Radiotherapy followed by PCV chemotherapy
  – Radiotherapy with concurrent TMZ followed by TMZ chemotherapy

• Anaplastic astrocytoma - Type 3 (Absence of IDH mutation)
  – Radiotherapy with concurrent TMZ followed by TMZ chemotherapy
Ongoing Clinical trials

- **CATNON** (Phase III trial of concurrent and adjuvant TMZ chemotherapy in non-1p/19q deleted anaplastic glioma)
  - Radiotherapy only
  - Radiotherapy and concurrent TMZ
  - Radiotherapy and TMZ four weeks later
  - Radiotherapy, concurrent TMZ, and TMZ four weeks later

- **CODEL** (Phase III intergroup study of TMZ alone versus RT with concurrent and adjuvant TMZ versus RT with adjuvant PCV chemotherapy in patients with 1p/19q co-deleted anaplastic glioma)
  - RT followed by PCV
  - RT + TMZ followed by TMZ
  - TMZ alone
Glioblastoma - Initial Treatment

- Maximum safe resection
- Test tumor tissue for 1p/19q deletion, IDH mutation, and MGMT promoter methylation status
- Conventional, fractionated radiotherapy (RT)
- RT with concurrent temozolomide (TMZ) chemotherapy
- Post-RT TMZ chemotherapy for 6-12 months
Temozolomide

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

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

PCP=Pneumocystis carinii pneumonia.
<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 mns</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 mns</td>
<td>1.8%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>MGMT methylated TMZ</td>
<td>23.4 mns</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 mns</td>
<td>23.9%</td>
<td>7.8%</td>
<td>7.8%</td>
<td>5.2%</td>
</tr>
</tbody>
</table>
63 y/o man presented with hemiparesis -treated with TMZ + radiotherapy -post-RT MR revealed worsened contrast enhancement
Post-surgery  Post-RT  2 months later  1.5 years later
Pseudoprogression

- Since the introduction of combination chemotherapy + radiotherapy, there has been increasing awareness of progressive and enhancing lesions on post RT imaging.

- This is usually not tumor progression, but treatment effect.

- Estimated to occur in 25%-40% of patients treated with RT with concurrent TMZ.

- These lesions are often asymptomatic and may decrease or stabilize in size without a change in treatment.

- May be a positive prognostic sign?
Optune (Novo TTF)

- Tumor Treating Fields (TTFields) therapy is a locally delivered treatment that uses electric fields to disrupt rapid cell division exhibited by cancer cells.
- The NovoTTF™-100A System is currently approved as a treatment for adult patients with glioblastoma following tumor recurrence.
- EF-14: RT/TMZ → TMZ+TTF (n=466) vs. TMZ (n=229)
  - Planned interim analysis 1.5 years after 315th patient enrolled. Benefit maintained when including all 700 pts (although 57% alive and 48% with no tumor progression)

<table>
<thead>
<tr>
<th>Overall survival</th>
<th>TTF</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (months)</td>
<td>19.6</td>
<td>16.6</td>
</tr>
<tr>
<td>2-year</td>
<td>43%</td>
<td>29%</td>
</tr>
</tbody>
</table>

- Pros = Minimal side effects
- Cons = continuous treatment (minimal breaks), requires fully shaved head, stimulator and battery pack necessary
Outline

• Immunotherapy
  – EGFR vIII: EGFR mutation variant III
  – Immune Checkpoint Inhibitors

• Radiotherapy
  – History of radiotherapy
  – New technologies
EGFR Mutation Variant III (EGFRvIII)

• Highly tumor-specific oncogene expressed in in 30% of primary GBMs
  – EGFRvIII+ GBM has shorter survival

• Rindopepimut (CDX-110): EGFR-vIII peptide vaccine conjugated to Keyhold Limpet Hemocyanin
  – Generates specific immune response against EGFRvIII-expressing GBM
  – Intradermal injection, most common side effect is injection site reaction
  – February 2015: FDA Breakthrough Therapy Designation
    • Expediting review for possible FDA approval
EGFRvIII+ GBM Trials

• Newly diagnosed GBM: Single-arm phase II studies (vs. matched EGFRvIII+ controls not receiving rindopepimut)
  – ACTIVATE\(^1\): 18 pts, median survival 26.0 mos (vs. 15.0 mos in control)
  – ACT II\(^2\): 22 pts, median survival 23.6 mos (vs. 15.0 mos in control)
  – ACT III\(^3\): 65 pts, median survival 24.6 mos (vs. 15.2 mos in control)

• ReACT: Recurrent GBM (no prior bevacizumab):
  – Randomized phase II of bevacizumab +/- rindopepimut
  – Rindopepimut improved survival from 9.3 mos to 11.6 mos\(^4\)

• ACT IV: Randomized, placebo-controlled phase III study for newly diagnosed EGFRvIII+ GBM
  – Trial closed December 2014, interim results expected soon

\(^1\)Sampson et al. J Clin Oncol 2010
\(^2\)Sampson et al. Neuro Onc 2011
\(^3\)Schuster et al. Neuro Onc 2015
\(^4\)Reardon D et al. ASCO 2015
Immune Checkpoint Inhibition

Ipilimumab blocks CTLA4

Nivolumab blocks PD1
Adverse Events with Checkpoint Inhibitors

**Gastrointestinal**
- Signs and symptoms such as:
  - Diarrhea
  - Abdominal pain
  - Blood or mucus in stool
  - Bowel perforation
  - Peritoneal signs
  - Ileus
  - Fever
- In symptomatic patients, rule out infectious etiologies
- Consider endoscopic evaluation for persistent or severe symptoms

**Liver**
- Signs such as:
  - Abnormal liver function tests (eg, AST, ALT) or total bilirubin
- Rule out infectious or malignant causes
- Increase frequency of LFT monitoring until resolution

**Skin**
- Symptoms such as:
  - Pruritus
  - Rash
- Unless an alternate etiology has been identified, signs or symptoms of dermatitis should be considered immune-mediated

**Neurologic**
- Symptoms such as:
  - Unilateral or bilateral weakness
  - Sensory alterations
  - Paresthesia

**Endocrine**
- Signs and symptoms such as:
  - Fatigue
  - Headache
  - Mental status changes
  - Abdominal pain
  - Unusual bowel habits
  - Hypotension
  - Abnormal thyroid function tests and/or serum chemistries
  - Hypophysitis
  - Adrenal insufficiency (including adrenal crisis)
  - Hyper- or hypothyroidism
  - Nonspecific symptoms which may resemble other causes (eg, brain metastasis)

**Other Adverse Reactions, including ocular manifestations**

---

*In a limited number of patients, hypophysitis was diagnosed by imaging studies through enlargement of the pituitary gland.

**NRG BN002**

**Patients with newly diagnosed GBM or gliosarcoma**
- KS ≥ 70
- Age ≥ 18 years
- Tissue available

**Radiation**
- (60 Gy in 2 Gy fractions)

**Concurrent daily TMZ**
- (75 mg/m² qd x 42 d)

**Stratify by MGMT and RPA OR MCP**

**Important Points:**
1. Primary endpoint: Overall Survival
2. Randomized phase II with early estimate of efficacy – potential expansion to phase III if estimate hits target
3. Pick “best” of 3 experimental arms: OS>toxicity>NCF>symptom burden

**ARM 1**
- TMZ (200 mg/m²) d 1-5 of 28-d cycle + Placebo Ipi (q 4wks) + Placebo Nivo (q 2wks)

**ARM 2**
- TMZ (200 mg/m²) d 1-5 of 28-d cycle + Placebo Ipi q 4wks) + Nivolumab (1 mg/kg q2wks)

**ARM 3**
- TMZ (200 mg/m²) d 1-5 of 28-d cycle + Ipilimumab (3 mg/kg q 4 wks) + Placebo Nivo (q 2 wks)

**ARM 4**
- TMZ (200 mg/m²) d 1-5 of 28-d cycle + Ipilimumab (3 mg/kg q 4 wks) + Nivolumab (1 mg/kg q 2 wks)

**Longitudinal determination of survival, neurocognitive function and symptom burden**

**PI:** Dr. Mark Gilbert
Our Current Approach

- Maximally safe surgery
- Radiotherapy
- Temozolomide
  - Temozolomide for glioblastoma
  - Temozolomide or PCV for grade III glioma
- Emerging role for Optune

→ The only treatments that have impacted survival

Can we improve upon what already works?
Radiotherapy for High-Grade Gliomas

46 Gy to microscopic disease

60 Gy boost to surgery cavity
Dose Escalation for Malignant Glioma

• How did we arrive at 60 Gy? Survival benefit
  – Walker et al. 1979: 420 pts on Brain Tumor Cooperative Group protocols, survival prolongation with 50-60Gy vs. lower doses
  – MRC trial (Bleehen, 1991): survival prolongation with 60 Gy vs. 45 Gy

• Dose escalation beyond 60 Gy
  – Phase III trial (Nelson, 1988): 70Gy vs. 60 Gy
  – RTOG 83-02: Hyperfx BID RT to escalate dose
  – RTOG 93-05 (Souhami, 2004): 60 Gy RT +/- radiosurgery
  – Laperriere et al., 1998: 50 Gy RT +/- I-125 implant

Studies conducted in nitrosurea era

No survival benefit
The Era of Temozolomide

Role of RT dose-escalation in the temozolomide era?
Intensity Modulated Radiotherapy

• As the treatment head arcs, leaves open and close to control the amount of radiation delivered

• This creates the ability to tightly sculpt dose.
Dose Escalation in the TMZ Era

- University of Michigan phase I/II trial
  - RT dose escalation (66 Gy to 81 Gy/6 weeks) with TMZ
  - N=38, late CNS grd 3+ toxicity at 78 Gy (2/7 pts) and 81 Gy (1/9 pts)
  - MTD: 75 Gy in 30 fractions
    - Zero of 22 pts had RT necrosis
  - Median OS: 20.1 mos (14.0-32.5 mos);
    Median PFS: 9.0 mos (6.0-11.7 mos)
  - Probability of 95% IDL failure decreased with increased RT dose ($p=0.05$)

Hypothesis: Local Therapy Intensification Alters Patterns of Failure

NRG BN001: NCI-Sponsored Trial

Basic Eligibility: Newly dxed GBM; Residual tumor/postop cavity ≤ 5cm; KPS > 70

Sample Size: 576 patients
Primary endpoint: Overall survival

Principal Investigators:
- Minesh P Mehta (UMaryland)
- Vinai Gondi (Northwestern Med)

Currently open:
1) University of Chicago
2) Northwestern Medicine (Downtown)
3) Northwestern Medicine (Warrenville)
4) Stoger Hospital of Cook County

Stratify

RPA

MGMT

Randomize

Dose-Escalated Radiotherapy
75 Gy + TMZ

Standard-Dose Radiotherapy
60 Gy + TMZ
IMRT versus Proton Therapy
NRG BN001: IMRT vs. Proton Therapy

• Radiotherapy dose-escalation arm:
  – Institutions with access to proton therapy:
    RT dose-escalation delivered with proton therapy
    • Northwestern Medicine Warrenville, Washington University
    • Upcoming: MD Anderson, Mass Gen Hospital, MSKCC
  – Institutions without access to proton therapy:
    RT dose-escalation delivered with IMRT

• Radiotherapy control arm:
  – Delivered with standard radiotherapy
NRG BN001: IMRT vs. Proton Therapy

• Hypothesis: In sparing more brain tissue, proton therapy improve upon IMRT in terms of:
  – Neurocognitive function
  – Quality of life
  – Overall survival
  ➔ Reducing RT effects on circulating lymphocytes
Conclusions

• Management of malignant/high-grade tumors is
  – Highly complex
  – Multi-disciplinary requiring expertise from …
    Neurosurgery
    Neuro-Oncology
    Radiation Oncology
  – Enhanced by ongoing new developments such as …
    • Novel therapies
    • Innovative clinical trials
  – Focused on enhancing patient’s quality and duration of life