Primary Brain Tumors

• The leading cause of cancer-related deaths in children
• The ~4th leading cause of cancer-related deaths in people under the age of 54
• Significant increase in incidence in people over the age of 60 years old (?
  screening artifact)
• A number of different types of brain tumors
  • Progress has been made in several less common types of brain tumors (i.e. germinoma, embryonal, PCNSL)
  • Less progress in gliomas: the most common primary brain tumor
Human Brain Tumors: Simplified Classification

- Primary brain tumors
  - Gliomas (e.g., astrocytomas)
  - Embryonal tumors (e.g., medulloblastoma)
  - Others (e.g., lymphoma, germ cell)
- Tumors of the coverings of the brain
  - Meningioma
- Tumors of peripheral nerve
  - Schwannoma
  - Neurofibroma
- Metastases
Human Brain Tumors: Simplified Classification

- Primary brain tumors
  - Gliomas (e.g., astrocytomas)

“Benign” gliomas, WHO grade I
(e.g., pilocytic astrocytoma)
Human Brain Tumors: Simplified Classification

- Primary brain tumors
  - Gliomas (e.g., astrocytomas)

  "Benign" gliomas, WHO grade I
  (e.g., pilocytic astrocytoma)

  Malignant gliomas, WHO grades II - IV
  (e.g., anaplastic oligodendroglialoma, glioblastoma)
# Malignant Gliomas

<table>
<thead>
<tr>
<th>WHO II</th>
<th>astrocytoma</th>
<th>oligo-astrocytoma</th>
<th>oligodendroglioma</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO III</td>
<td>anaplastic</td>
<td>anaplastic</td>
<td>anaplastic</td>
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<tr>
<td></td>
<td>astrocytoma</td>
<td>oligo-astrocytoma</td>
<td>oligodendroglioma</td>
</tr>
<tr>
<td>WHO IV</td>
<td>glioblastoma</td>
<td></td>
<td></td>
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</tbody>
</table>
# Malignant Gliomas

<table>
<thead>
<tr>
<th>WHO Grade</th>
<th>Tumor Type</th>
<th>Age Range</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO II</td>
<td>astrocytoma</td>
<td>3-10 yrs</td>
<td>? %</td>
</tr>
<tr>
<td></td>
<td>oligo-astrocytoma</td>
<td>5-12 yrs</td>
<td>? %</td>
</tr>
<tr>
<td></td>
<td>oligodendroglioma</td>
<td>8-20 yrs</td>
<td>? %</td>
</tr>
<tr>
<td>WHO III</td>
<td>anaplastic astrocytoma</td>
<td>2-5 yrs</td>
<td>10-30 %</td>
</tr>
<tr>
<td></td>
<td>anaplastic oligo-astrocytoma</td>
<td>2-8 yrs</td>
<td>20-60 %</td>
</tr>
<tr>
<td></td>
<td>anaplastic oligodendroglioma</td>
<td>2-10 yrs</td>
<td>40-80 %</td>
</tr>
<tr>
<td>WHO IV</td>
<td>glioblastoma</td>
<td>1-2 yrs</td>
<td>10 %</td>
</tr>
</tbody>
</table>
Diffuse Astrocytoma
WHO Grade II

Anaplastic Astrocytoma
WHO Grade III

Lantos PL, Louis DN, Rosenblum M, Kleihues P.
Tumours of the nervous system. In: Greenfield’s Neuropathology, 2002
Oligodendroglioma and Anaplastic Oligodendroglioma
Oligodendroglioma and Anaplastic Oligodendroglioma
Glioblastoma

Lantos PL, Louis DN, Rosenblum M, Kleihues P.
Tumours of the nervous system. In: Greenfield’s Neuropathology, 2002
Glioblastoma

Lantos PL, Louis DN, Rosenblum M, Kleihues P.
Tumours of the nervous system. In: Greenfield’s Neuropathology, 2002
Low Grade Gliomas: Treatment

• “Complete” surgical resection generally considered optimal
• Radiation therapy can halt disease progress for a time; probably increases survival.
  • Timing, dose, volume remain unresolved
  • Long-term neuro-cognitive deficits are a significant concern
• A growing interest, particularly in oligodendrogliomas, in the use of chemotherapy (temozolomide) in order to delay radiotherapy.
  • Radiographic responses possible
  • No long term data
High-Grade Gliomas: Treatment

• “Complete” surgical resection generally considered optimal
• Radiation therapy is the foundation of treatment.
  • Involved field
  • 6000 cGy over 30 fxs
  • Long-term neuro-cognitive deficits less a concern secondary to short survival

• Chemotherapy
  • 3 meta-analyses show small survival benefit in the post-radiation setting
  • Temozolomide administered with XRT and post XRT increase median survival by ~2.5 months and 2 year survival by ~18%.

• BCNU-Impregnated Wafers (“Gliadel”)
  • Increase median in recurrent resected GBMs by ~ 5 weeks.
  • Increases median survival in newly diagnosed GBMs by ~4 weeks
Ineffectiveness of Current Treatment for Malignant Gliomas

- No treatment: 3 months median survival
- Surgery: 4 month median survival  
  - Limited by infiltrative nature of tumor
- Radiation (+ Surgery): 10 months median survival  
  - Only proven benefit
  - Limited by toxicity to normal CNS tissue and
  - Limited by relative radiation resistance of gliomas
- Chemotherapy (+ XRT/surgery): 14 month median survival:  
  - Limited by drug delivery (Blood-brain barrier)
  - Limited by intrinsic and acquired chemotherapy resistance
Brain Tumors Differ from Systemic Tumors: Obstacles to Developing Effective Glioma Therapies

- Unique microenvironment (CNS)
  - Sensitive/non-expendable tissue
  - Physiologically different than other tissues (i.e. pH, ECM components).
- Alternate endothelial biology (anti-angiogenesis)
- No lymphatic system
- Immunological sanctuary
- Biology
  - Acquired and intrinsic drug resistance
  - Different signaling pathways in neuro-ectodermally derived tumors
- Non-metastatic: infiltrative growth characteristics of gliomas
Issues In Glioma Clinical Trials:

• **Pharmacology**
  - Hepatic cytochrome P450 isoenzymes are induced or inhibited by many anti-epileptic drugs (e.g. dilantin, tegretol, phenobarbitol)
    - P450s involved in chemotherapy metabolism.
  - Patients on enzyme-inducing anti-epileptics have significantly altered drug metabolism (e.g. MTD of Taxol and CPT-11 > 3 fold higher).
  - Clinical trials need to establish two different MTDs; for patients on EIAEDs and for those not on EIAEDs.
Issues In Glioma Clinical Trials

• Patient heterogeneity
  • Variable prognostic factors
    ✓ Age
    ✓ Performance Status
    ✓ Extent of resection
    ✓ Neurological deficits (mini-mental exam)
    ✓ Glucocorticoids
Issues In Glioma Clinical Trials

- Tumor heterogeneity
  - Variable histologies (astro, oligo, mixed)
  - Inter-observer variability
  - Variable grade
    - ? grading a recurrent treated glioma
  - Anatomic location of tumor (i.e. brainstem)
  - Different biology
    - Alternate genetics
      - Primary vs. secondary GBM
      - 1p/19q deletions in oligos
      - HMGТ status?
Issues In Glioma Clinical Trials: Historical Data

• Literature is severely flawed
• Investigator-selected criteria for response (almost always includes stable disease)
• Often no requirement for response duration
• Often no control of glucocorticoid or MRI technology
• Often no control for important prognostic factors (i.e. tumor type, grade)
• Current data bases being generated by NCI sponsored brain tumor groups (NABTC, NABTT, PBTC, RTOG) will improve the objective nature of neuro-oncology trials but they are currently not freely available.
  • Patients on consortia/cooperative group trials may not be representative of the average community patient.
• With possible recent exception of radiation (+/- temozolomide), no agreed upon standard of care to base a comparison on.
Clinical Meaningful Endpoints for Patients with Brain Tumors

- Survival
- Disease stabilization
- Clinical Response
- Radiographic response
- Quality of life
**Glioma Trials: Efficacy Endpoints**

- **Survival:**
  - **Advantages**
    - Objective
    - Clinically meaningful
  - **Disadvantages**
    - Requires large randomized studies in a rare disease
      - No adequate historical controls for non-randomized comparisons except for RTOGs recursive partition analysis for newly diagnosed malignant gliomas
      - Small number of tumors make it very difficult to study any glioma subtype except GBM
    - Difficult to balance hugely important prognostic factors, particularly in the recurrent setting
      - Difficult for approving drugs in the recurrent setting
      - Does not allow approval for palliative drugs
Glioma Trials: Efficacy Endpoints

- **Disease stabilization (i.e. PFS, TTP)**
  - **Advantages**
    - Shorter time to data maturation
    - Since tumor progression is usually associated with worsening neurological function, tumor stabilization might translate to improved QOL…but, no data
  - **Disadvantages**
    - How much time does it really save vs. survival endpoint
    - Not validated as a surrogate for survival
    - Requires large randomized studies in a rare disease
      - No adequate historical controls for non-randomized comparisons
      - Small number of tumors preclude study of all gliomas except GBM
    - Difficult to balance hugely important prognostic factors
      - RTOG Recursive Partition Analysis
      - Particularly difficult to balance prognostic factors in the recurrent setting
        - NCI Brain Tumor Consortia attempting to develop a historical data base for this purpose
      - Does not allow approval for palliative drugs (i.e. a steroid replacement/glucocorticoid)
Glioma Trials: Efficacy Endpoints

• **Clinical Response:**

  • **Advantages:**
    ✓ Associated with patient symptoms, performance and QOL
  
  • **Disadvantages:**
    ✓ Symptoms subjective
    ✓ Neurological signs are objective but significant inter-examiner variability
    ✓ Affected by other concomitant medications/medical conditions:
      – Glucocorticoids
      – Anti-epileptics
      – Anti-coagulants
Glioma Trials: Efficacy Endpoints

• Radiographic Response

• Advantages:
  ✓ Objective (somewhat)
  ✓ Historical standard

• Disadvantages
  ✓ Many caveats
Glioma Trials: Efficacy Endpoints

Radiographic Response:

- **Caveats**
  - MRI standard (CT scan, brain scans, angiography and myelography largely outdated; PET scans and MR spectroscopy give supplemental but not definitive data).
  - Since gliomas usually do not form “lumps” in the brain, MRI scans are often not looking at tumor directly, but rather the effects of tumor on the normal microanatomical, vascular and chemical architecture of the brain.
  - Tumors cause several different signal abnormalities on MRI scans:
    - T2 signal intensity: represent vasogenic edema associated with tumor; cystic fluid, necrosis, CSF leakage
    - FLARE signal abnormality represents vasogenic edema, cerebrum infiltrated by tumor, necrosis
    - TI signal hypointensity: cerebral edema, cerebrum infiltrated by tumor
    - T1 signal hyperintensity: blood
    - Gadolinium enhancement: disruption of the BBB
Principles of MR- Gd- Contrast Agents

blood flow

extracellular space

intracellular space

Tumor cell

Capillary wall

Erythrocyte

Gd-chelates

diffusion in extracellular space

rediffusion into the intravascular space
Glioma Trials: Efficacy Endpoints

Radiographic Response:

- **Caveats**
  - Almost all clinical trials measure gadolinium enhancement as response criteria. There are several problems with this:
    - ✔️ Does not measure non-enhancing tumors or portions of enhancing tumor that do not enhance.
    - ✔️ One is not necessarily measuring tumor but rather only vascular permeability.
    - ✔️ Factor besides tumor effect vascular permeability:
      - GLUCOCORTICOIDS
      - Radiation damage
        » Acute (i.e. immediate post-radiation)
        » Subacute/chronic
        » Necrosis
      - Vascular stabilizing drugs can cause decrease enhancement
      - Amount of gadolinium enhancement dramatically effected by MRI machinery and technique for gadolinium administration (non standardized).
Glioma Trials: Efficacy Endpoints

Radiographic Response:

- **Caveats**
  - Tumors grow infiltratively in 3 dimensions associated with cyst formation and necrosis: No agreed upon way to measure the gadolinium enhancement
    - Uni-dimensional
    - Bi-directinoal
    - Volumetric
    - RECIST Criteria not validated for brain tumors
  - Two general methodologies utilized
    - “McDonald Criteria”
    - “Levin Criteria”
Clinical Meaningful Endpoints for Patients with Brain Tumors

- **Survival**
  - Absolutely,
    - Assuming treatment-related toxicity is not prohibitive
- **Progression free survival**
  - Only if a surrogate for some other clear clinical benefit
- **Radiographic response**
  - Only if a surrogate for some other clear clinical benefit
- **Clinical response/Quality of life**
  - Maybe
    - What are the metrics for brain tumor patients?
Clinical Meaningful Endpoints for Patients with Brain Tumors

• Quality of Life/Patient-Related Symptoms
  • Neurological function
    ✓ Motor (ambulation, strength)
    ✓ Sensory (vision, hearing)
    ✓ Cognitive
    ✓ Increased independent living
  • Delay in neurological morbidity
  • Decreased seizures
  • Decreased decadron requirements

Tools for measuring metrics are unclear
**Glioma Clinical Trials: Conclusion**

- Few effective treatments: therapy remains largely suboptimal.
- No systemic therapy approved for recurrent GBM.
- No historical data base; past literature largely undependable.
- Evaluation of clinical trials effected by patient and tumor heterogeneity; factors shown to have greater impact on patient outcome than any given therapy.
- Survival is the only trial endpoint that is clearly accepted.
- A treatment that results in tumor and symptom stabilization would be considered clinically meaningful and useful; but how best to objectively measure such an outcome remains unclear.
Two Basic Questions:

What therapeutic outcomes are truly clinically meaningful to patients with gliomas?

What clinical trial endpoints are representative of those outcomes and how do we objectively and reproducibly measure them?