Central Nervous System Tumors

Heterogeneous group of primary tumors
Approx 17,500 cases diagnosed/year
Majority are glial- astrocytic, oligodendrogial, ependymal
Malignant glioma, grade III and IV, are most common
Median survival for GBM is 12-15 months with multimodality therapy
Great need for novel therapeutic strategies

Molecular Epidemiology

Markers of Exposure

Exposure
Internal Dose
Bio Effective Dose
Early Bio Effect
Altered Structural Func
Clinical Cancer
Progression

Markers of susceptibility/resistance
Intervention opportunities

Cancer and Precancer Markers

Genetics Genomics
Biomarkers
Transcriptomics
Proteomics
Metabolomics

After Molecular Epidemiology, Schulte & Perera

Neuro-Imaging

Physiologic/functional imaging

PET
pMRI
1H MRS

Anatomic Imaging

After Neuro-Imaging research, Physiologic/functional imaging
MR Spectroscopy

Tumor burden by MRI+MRSI  
MRS predicts tumor relapse prior to MRI

MRI predicts progression, MRSi predicts primarily necrosis

Patient Outcomes Research

Cancer Care and Survivorship
  - Quality of Life
  - Symptom Clusters
  - Cognitive Function
  - Caregiver Research
  - Education

Neuro-Oncology Therapeutic Clinical Trials

Efficient and accurate evaluation of novel therapies
Determine true benefit of therapy while maximizing resources- patients, time, financial, personnel effort
Phase I- toxicity studies
Phase II- preliminary efficacy studies
Phase III- improvement in patient outcomes over standard therapy

Surgery for Glioma

Maximal, safe resection to achieve the following goals
1) Relieve mass effect and improve symptoms
2) Provide tissue for histological diagnosis, molecular and cytogenetic analysis
3) Improve survival

Techniques for maximal, safe resection

Most reports of techniques have been retrospective reviews of single institution experience
- Pre-operative functional mapping using diffusion tensor imaging
- Intra-operative motor and speech mapping
- Intra-operative imaging

Subcortical White Matter Tracts using DTI
Surgery for Glioma

Surgery to extend survival ("cytoreduction") - the most controversial of the three goals
No randomized trials completed or planned -- size of such a trial would be substantial
Nonrandomized trials all suffer from selection bias - tendency for favorable patients to undergo resection
Definition of surgical margins and assessment of extent of resection ??

Clinical Trials - Radiation

Standard radiation therapy for GBM - 60 Gy administered in 2Gy fractions over 30 treatments to tumor and 2 cm margin
Strategies to increase dose to tumor while sparing normal tissue
Previous studies of focal radiation with radiosurgery or brachytherapy did not show a survival advantage in GBM
Accelerated radiotherapy has not resulted in improved survival

Clinical Trials - Cytotoxic agents

Meta-analysis of nitrosourea in malignant glioma trials suggest modest improvement of survival
In late 1980s, chemosensitivity of anaplastic oligo / oligoastro was one of the most exciting developments in neuro-oncology
High correlation between 1p/19q loss (both alleles) and radiosensitivity, chemosensitivity

Surgery for malignant glioma

Stummer et al (Lancet Oncol:5/06)
Phase III study of fluorescence guided surgery with 5-aminolevulinic acid (5-ALA) for resection of malignant glioma
322 pts who were selected for GTR were randomized
GTR achieved in 65% pts who received 5-ALA vs 36% who did not
6 month PFS was 41% vs 21%
Post-op neurologic complications similar
Effect on survival was not a primary outcome
Surgeons were not blinded to treatment group

Clinical Trials - Radiation

Role of intensity modulated radiotherapy being evaluated
Radiosensitizers have not afforded a survival benefit
? Role of targeting treatment using physiologic imaging
? Approaches to reduce radiation injury - hyperbaric oxygen

Anaplastic oligo / OA

Two important RCTs published in June 2006 (JCO) compared XRT plus PCV chemo to XRT alone (either neoadjuvant or adjuvant)
Both trials found modest difference in progression-free survival, with no difference in overall survival
CTX failed to provide benefit regardless of 1p/19q status
Anaplastic O/OA: RTOG 9402

Mechanism of loss of both chromosomal moieties now known to be due to formation of a derivative chromosome through translocation of long arm of 1 plus short arm of 19
Reason this affects clinical course still unknown

Jenkins RB Cancer Res (Oct 2006)

Based on the results of these studies, future clinical trials of grade III tumors will stratify treatment based on 1p 19q deletion status
Redefines eligibility of patients based on molecular profiling rather than standard histology
Highlights the importance of tissue acquisition to assess patients for clinical trials
**Clinical Trials - Cytotoxic agents**

Findings of genetic marker (O6-methyl guanine-DNA methyltransferase (MGMT) that affects temozolomide sensitivity

Optimal scheduling of standard chemotherapy such as temozolomide being evaluated

Strategies to reverse drug resistance being pursued

Ongoing RTOG 0525 study

Newly diagnosed GBM randomized to XRT/temo and either standard adjuvant versus dose dense temozolomide

MGMT status evaluated in all patients

**Clinical Trials - Targeted agents**

Knowledge of dysregulated signaling pathways in glioma allow for selection of targeted therapies

Signal transduction agents are drugs that target a specific signal/switch pertaining to:

- Tumor cell proliferation
- Tumor cell survival/apoptosis
- Angiogenesis
- Invasion/migration

May target surface receptors, tumor microenvironment or tumor vasculature

**Signaling Pathways and Therapeutics**

- Monoclonal Antibody
- Enzyme Inhibitors
- Signal Transduction
- Gene Transcription

Targeting abnormal signaling pathways – Combinatorial Strategies
Challenges in the evaluation of targeted agents

- Determination of optimal biological dose rather than maximal tolerated dose
- Selection of target to be modulated and appropriate agent
- Assessment of activity: modulation of target and clinical benefit
- Standard assessment of tumor response inadequate - e.g., anti-VEGF agents target the abnormal tumor vasculature and can normalize the BBB thereby resulting in an immediate and dramatic decrease in enhancement which is not a measure of antitumor effect

Multimodality Therapy

- Advantage of different mechanisms of antitumor effect
- May have non-overlapping toxicities - safe administration of combinatorial treatments
- Synergistic effect with cytotoxic agents/radiation being explored
  - e.g., Bevacizumab/CPT11: results of a phase II study showed RR of 60% and 6 mo PFS of 39%

Limitations of therapy for malignant glioma

- Surgery
  - Due to the infiltrating nature, complete resection is difficult
- Radiation
  - Dose is limited by secondary brain injury
- Chemotherapy
  - Inadequate delivery of drug to tumor
  - Drug resistance
  - Systemic side effects

Strategies to improve delivery of drugs into the brain

A. B. C. D.

Interstitial therapy

- Direct intracavitary or interstitial therapy continues to be investigated
- Chemotherapy impregnated biodegradable wafers (carmustine, SFU)
- Radiation (I131 labeled antitenascin monoclonal antibody, gliasite delivery)
- Novel agents (TNF-alpha, liquid crystalline chemotherapy, I-131 TM-601 or scorpion venom)
Convection-Enhanced Delivery (CED)

CED studies

Agents tested include:
- Chemotherapy (paclitaxel)
- Conjugated toxins (IL13-pseudomonas exotoxin, transferrin/diptheria toxin, TGF alfa pseudomonas exotoxin)
- Antisense oligonucleotides- (TGF-beta2 mRNA)
- Radioactive monoclonal antibodies

Planned studies:
- Viruses
- Nanoliposomal agents

Challenges include optimal catheter placement and delivery and assessment of volume of distribution of agent.

These surgically based studies highlight the importance of the involvement of the neurosurgeon in the design, development, conduct and evaluation of these trials.

Other experimental treatment approaches

- Gene therapy approaches
  - Using viruses that can and cannot replicate
- Use of neural stem cells
  - Delivery of therapeutic agents
  - Conversion of prodrugs
- Immunotherapy trials
  - Nonspecific activation of the immune system
  - Activation of cellular immune response
  - Using antibodies directed at specific tumor antigens (autologous tumor dendritic cell vaccine, heat shock protein vaccine)

UCSF Neuro-Oncology Clinical Trials

Newly diagnosed disease
- Phase II Temozolomide for Low Grade Glioma
- Enzastaurin for GBM - Eli Lilly Phase I/II
- RTOG 0525 for GBM- standard adjuvant temodar vs dose intense temodar

Recurrent Malignant Glioma
- Phase II Heat Shock Protein Vaccine
- NABTC studies for recurrent disease
  - NABTC 03-02 (Clenogide)
  - NABTC 03-03 (Depesipptide)
  - NABTC 04-01 (GW)
  - NABTC 04-02 (OSi/CCI)
  - NABTC 04-03 (SAHA/Tmz)
  - NABTC 05-02 (Bay+ OSi/CCI/R11)
  - NABTC 06-01 (VEGF-trap)
Neuro-Oncology Clinical Research

Continued need for the advancement in understanding of the scientific basis of glioma formation
Insight into molecular biology and cytogenetics important for translation to the clinic
Evaluation of novel therapies required
Quality of Life studies important in conjunction with therapeutic trials
Cooperative and multidisciplinary effort essential

Neuro-Oncology Clinical Research

Role of the neurosurgeon is critical to the success of clinical research in Neuro-Oncology:

Development of standard operating procedures for intraoperative high quality tissue acquisition for molecular and cytogenetic characterization (NIH- cancer genome atlas initiative and the glioma molecular diagnostic initiative)
Tissue is important for assessment of biomarkers for diagnosis, prediction of response, prognosis, selection of patients for clinical trials

Real-time Neuro RSP: Radiology, Surgery, Pathology

Tissue arrays

Distinctive Molecular Profiles of High-Grade and Low-Grade Gliomas based on Oligonucleotide Microarray Analysis. Rickman et al Cancer Research 2001

Neuro-Oncology Clinical Research

Role of the neurosurgeon is critical to the success of clinical research in Neuro-Oncology:

Identification of important surgically based questions for malignant glioma with plan for prospective evaluation

Standardization of surgical procedures for relevant clinical trials e.g. CED

Translational effort of many neurosurgeon clinician/scientists to design, develop, conduct and evaluate prospective therapeutic surgically based clinical trials