

CNS Tumors: The Med Onc Perspective

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Disclosure

- Speakers Bureau, Merck

Basic Oncology Concepts

- Tissue Diagnosis
- Stage of Dz
- Performance Status of Patient (KPS, ECOG)
- Goals of Care (Palliative vs Curative)
- Systemic Therapy (vs Local Therapy)

Tissue Diagnosis

- Biopsy vs resection (exception: brainstem glioma)
- Histology: Primary CNS (23k per year in US) vs CNS Lymphoma vs Metastatic Dz
- Primary CNS: Astrocytoma vs Oligodendroglioma
- GRADE (World Health Org Gr I, II, III, IV)
- 'Low Grade' (I, II) vs 'High Grade' (III, IV)

Grade IV Astrocytoma

- AKA Glioblastoma Multiforme (GBM)
- Most common CNS tumor in adults
- Even after gross total resection, dz recurrence expected
- 5 year survival < 5 %
- ‘Adjuvant’ therapy after resection
- Grade III (‘Anaplastic’) Astrocytoma—treated similarly

Grade III-IV Astrocytoma: Post-op RT

- Study of 118 patients
- Randomized to RT (whole supratentorial) vs observation
- Median Survival 10.8 vs 5.2 months

- Kristiansen K et al. Cancer 1981 Feb 15; 47(4): 649-52.

Adjuvant Chemotherapy

- Several trials have demonstrated benefit
- Most important: Stupp Trial
- Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma. Roger Stupp, et al, N Engl J Med 2005; 352:987-996

Stupp Study

- 573 post-op GBM patients up to age 70.
- Pts randomized to daily temozolomide concurrently with RT followed by 'maintenance' temozolomide after RT X 6 cycles vs RT alone
- Median Survival 14.6 vs 12.1 months
- (What do we think of median survival as an endpoint?)

Stupp Study Outcomes

- Median Overall Survival: 14.6 mos vs 12.1 mos
- 2 year survival: 26.5% vs 10.4%
- 5 year survival: 10% vs 2%

Stupp Study Questions

- What's more important, concurrent temodar or maintenance temodar?
- Number of maintenance temodar cycles?
- PCP prophylaxis necessary?
- Is there a way to predict who will respond best to the use of temodar with RT?

MGMT hypermethylation

- O-6-MethylGuanine-DNA-MethylTransferase
- Gene for enzyme involved in DNA repair
- Hypermethylation of promotor region of the gene reduces cell's capacity to repair damage from alkylators such as temozolomide
- Hypermethylated MGMT promoter=more susceptibility to damage from temozolomide

MGMT and Stupp Study

- MGMT promotor hypermethylated in 45% of 206 assessable tumors
- Among hypermethylated MGMT pts, benefit of receiving temozolomide: Median OS 21.7 mos vs 15.3 mos with RT alone
- Among nonmethylated patients, a smaller (not statistically significant) difference
- N Engl J Med. 2005 Mar 10;352(10):997-1003.

Conclusions re MGMT

- Hypermethylation of MGMT promotor is PREDICTIVE of response to temodar
- Also predictive of response to RT, and other chemotherapy agents (other studies)
- Is this test important?

2nd Line Chemotherapy for High Grade Astrocytoma

- Metronomic low dose daily temodar (26% 6 month progression free survival)
- BCNU (Carmustine)
- CCNU (Lomustine)
- PCV (Procarbazine, CCNU, Vincristine)
- Etoposide
- Carboplatinum

Bevacizumab

- Antibody to VEGF (vascular endothelial growth factor)
- Inhibition of angiogenesis
- IV dosing 10 mg/kg Q 2 weeks
- Phase II studies show efficacy in recurrent Gr III and IV astrocytoma

Bevacizumab trial

- 167 pts with recurrent GBM
- Randomized to bev +/- irinotecan chemotherapy
- Response rate: 28% vs 38%
- Median survival 9.2 mos vs 8.7 mos (not statistically significant)
- Friedman HS et al, J Clin Onc 2009; 27: 4733-40

Assessing the Patient

- Clinical/neurologic symptoms
- MRI brain (with and without contrast)
- All brain scans: subject to interpretation!

Brain MRI pitfalls

- Pseudoprogression: when tumor LOOKS worse after chemo/RT, particularly during the first three months after chemo/RT, but it isn't worse. 'Radiation-induced vascular changes'
- Pseudoregression: when tumor LOOKS better after bevacizumab but it isn't better. Vascular changes have decreased contrast enhancement, that's all.

Side effects: Dexamethasone

- Gastric ulcer
- Fluid retention
- Hypertension
- Increased appetite
- Cushingoid changes (fat distribution, etc.)
- Wt gain
- Insomnia

Dex side effects, Cont'd

- Suppression of fever
- Psychosis
- Muscle wasting (bilat proximal weakness)
- Osteoporosis

Side Effects: Temozolomide

- Nausea/vomiting
- Alopecia?
- Myelosuppression (sequelae: infection, bleeding, and/or anemia): Check CBC!
- Aplastic Anemia
- Fatigue
- Rash
- Elevated LFTs
- ? Leukemiagenesis?

Side Effects: Bevacizumab

- Bev is a biologic agent, NOT a chemotherapy!
- NO nausea, NO myelosuppression
- Watch for HTN (treat it!)
- Proteinuria
- Abn bleeding (minor/major)
- Abn clotting (minor/major)
- Wound dehiscence

Questions