When Benign Tumors Go Bad: Emerging Medical Treatments

Erin M Dunbar, MD, Howard “Nick” C Chandler, MD
erin.dunbar@piedmont.org; cell: 1-404-858-7317

Piedmont Brain Tumor Center
No Relevant Disclosures

Slides are Available for Your Reference
CME Objectives are in your Conference Materials
Overarching Principle
Paucity of Evidenced-Based Medical Therapy

FOCUS: Using Best-Available Evidence For Individualized Goals of Care

Symptom-directed (palliative)

Tumor-directed
Symptom-directed Treatment

- Interdisciplinary Team!
- Infertility – counsel, grants
- Vision – monitor VF & VA
- Endocrine Treatments
- Cranial Nerve deficits
- Mass effect and vasogenic edema
- Seizures
- Thrombosis and hemorrhage
- Depression, coping
- Iatrogenic side-effects (from treatment)
First Things First
R/o Malignant Tumors

- **Consider Tumor Boards**
  - H&N, CNS

- **Example: Sella**
  - Germ cell tumors (ectopic pinealomas)
  - Chordomas
  - Primary CNS lymphoma
    - Must rule out metastatic systemic lymphoma
  - Metastatic disease (1-2% sellar masses)
    - Rarely, the 1st or only location
    - Migration alone nerves
Also, R/o Non-Tumors

- Cysts — Rathke's cleft, arachnoid, dermoid cysts
- Abscess — rare
- Arteriovenous fistula of the cavernous sinus
- Lymphocytic hypophysitis — Lymphocytic infiltration
  - Usually occurs in late pregnancy or the postpartum period
  - Infrequently in men
Select “Benign” Tumors with Emerging Medical Tumor-Directed Therapies Refractory to, or not Amenable to, Traditional Treatments
Olfactory Neuroblastoma Case Report

Pre-treatment maximal disease at the frontal lobes (A), cavernous sinus (B, C), and parotid lymph node (D), best imaged on T1-w MRI

- Palliative Avastin (targeting venous congestion) +/- TMZ
- Palliative Ommaya Reservoir

Dunbar, EM et al, Rare Tumors, 2012
Olfactory Neuroblastoma

Pre-Treatment

Post-Treatment (2 months to reach max)
Olfactory Neuroblastoma

Pre- and post-placement of Ommaya reservoir demonstrating maximal encephalocele size (A) and representative minimization (B) after cerebrospinal fluid draw.
Pituitary Adenomas or Carcinomas +/- secreting Case Series

- Watch precipitous endocrine effects (central DI)
- Temozolomide
  - Especially if Meth-MGMT, +MSH6
- Capecitabine (oral 5-FU) & Temozolomide
- Avastin
  - Especially if venous congestion or edema

Atypical or Malignant Meningioma Case Series

- Consider staging neck (LNs), spine (macroscopic), lungs
- No establishes systemic agent
- No significant activity with progesterones, interferon alfa-2b, Temozolomide, hydroxyurea, and chemo combos
- Somatostatin receptor analogs under investigation
  - Octreotide – stable disease > partial responses
- Molecularly Targeted Agents under investigation:
  - Anti-angiogenesis (PO, IV) – stable disease > partial responses – especially because of other effects
  - Platelet derived growth factor (PDGF)
  - Epidermal growth factor receptor (EGFR)
Rhabdoid Meningioma
Case Report

Pre-Treatment

Post-Tx (max clinical: 2 mo; max rad.: 3 mo)
Rhabdoid Meningioma
Case Report

- Palliative Avastin +/- TMZ
- Significant and Durable Response
- Off narcotics
- Gabapentin, Lyrica, Lidocaine patches....

Dunbar, EM, EJCMO 2011
Anti-angiogenic Agents Safety in CNS tumors

- **Toxicities:**
  - Extrapolated: Mets, Gliomas
  - (baseline % vs. AA for ~ 6-12 mo.)
- Arterial/venous thromboses (~2, <5%)
- Arterial/venous hemorrhage (~8, <10%)
- “Accelerates” CAD, CVD, PVD, Hypertension, Renal (protein, Cr.)
- Delayed wound healing/breakdown
- Fatigue
- Rare: reversible posterior leukoencephalopathy syndrome

FDA 2007: Bevacizumab (Avastin, VEGF-R monoclonal Ab) for progressed GBM

Widely extrapolated to recurrent, progressive tumors, radiation-necrosis, etc.!
Anti-angiogenic Agent Safety in CNS Tumors

- Surgical/Procedural safety: **ASK about AAs and ACs**!
- Elective: Hold for ~28 days for major, ~14 days for minor surgery/procedures (based on ½ life).
- Urgent/emergent: No reversal or antidote
- Usually no intra-op issues
- Consider conservative closure
- Close post-op monitor for delayed sequela (end of ½ life)
- Prophylaxis: Surveillance and avoid over AC
Temozolomide (Temozad, TMZ) Safety

- Remarkably well-tolerated
- Oral, various regimens
- cbc/diff, close communication
- **Thrombocytopenia - RARE** (essentially no anemia!)
- **Immuno-suppression – QUALITATIVE > quantitative** (lymphocytes >> neutropenia)
  - PJP prophylaxis (i.e., bactrim (sulfa allergy), dapsone, pentamadine)
- Nausea
- Constipation
- Fatigue
- Headache
Vestibular Schwannomas in NF2
Numerous retro/prospective case series

- Bevacizumab (Avastin)
- ~70% stable or retained hearing
- > 50% hearing improvement
- ~50% some tumor shrinkage in most lesions
- Delayed hearing loss, time to surgery,
- ? Neo-adjuvant, refractory?

Brain Tumor Center
Plotkin SR, NEJM, 09
NF-2: Meningioma, Schwannoma (Schwannomatosis), Plexiform Neurofibromas, PNSTs
Retrospective Case Series

• Schwannomas (VS, ? Others)
  – Bevacizumab (Avastin) as prior
  – VEGF pathway likely dominant driver of angiogenesis

• Meningiomas
  – Bevacizumab (Avastin)
  – Radiographic response in 29% of the meningiomas, but only avg. 3.7 months

• VEGF pathway NOT dominant driver of angiogenesis
• Comparable to sporadic meningiomas

NF-2: Meningioma, Schwannoma (Scwhannomatosiis), Plexiform Neurofibromas, PNSTs
Retrospective Case Series

- Consider Tumor Boards
- Consider Specialty Centers
- Consider Trials and Patient/Tissue Registries
- Possible synergy with surgery, SRS, RFA, u/s, etc.
- Watch for malignant transformation
- Whole-Body MRI and 18F-FDG-PET

Nunes, FP 2013; Urban T. 2012
Medical Treatment Selection

When/What New Treatment to Start:

1. General Science
2. General Safety
3. Goals/Wishes/Fears
4. Strategy
   i.e., Order of Therapy
5. Logistics
   - Oral, IV, Outpatient, inpatient
   - Cost/insurance
   - Frequency
   - Interested in a Trial? See next slide
   - Support required by others (drivers?)
   - Where located, available elsewhere?

Relatively, equally likely to be safe or work
What/When New Treatment to Stop:

1. Do you want it?
2. Is it Safe?
   - General medical or tumor/treatment-related
3. Is it getting the job done?
   - Based on pre-selected goals of care
Interested in a Trial?

A trial is a good idea that is unproven

• Types
  – Therapeutic
  – Supportive, quality of life
  – Outcome and risk factors
  – Tissue analysis

• Phases (Therapeutic)
  – Phase 1 – Safe?
  – Phase 2 – Work?
  – Phase 3 – Compare two existing therapies

• The overwhelming number of trials in brain cancer are negative, which means patients on the investigational arm of the trial either do “as well as” or “less well” than those on the standard arm
National Trial Listing

- 1. www.clinicaltrials.gov

Helpful instructions for performing a search:
- Click on “Search for Clinical Trials”
- Click on “Advanced Search”
- Scan down to Recruitment and choose “Open Studies” in the drop down menu
- Scan down to Study Type and choose “interventional studies” in the drop down menu
- Scan down to Conditions under “Targeted Search” and type in brain tumor
- You can then limit search by area (state) and by phase of study, as well. Please click on the highlighted word “Phase” for further definition of this term. After you have chosen all of your key terms/limits, you can click on “Search” at the bottom of the screen.
THE END

THANK YOU

Erin M Dunbar, MD; Howard “Nick” Chandler, MD
Erin.dunbar@piedmont.org; cell 1-404-858-7317
Piedmont Brain Tumor Center, Atlanta, GA, USA