Medical Complications of Brain Tumors and Symptom Management
Problems arising during and after treatment of brain tumors

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Common Problems
(and reasons for re-admission to the hospital)

1) Edema
   Steroid treatment and its complications
2) Seizures– how to treat and for how long– Dr. Davis’ territory!
3) Venous thromboembolism- how to avoid and how to treat
4) Infections– risks of shingles, pneumonia, urine infections
5) Adverse effects of chemotherapy
6) Mood, fatigue
7) Long-term complications after brain tumor therapy-→ the broadening scope of palliative care
Team Goals:

Choose the best treatment for the patient’s personal situation

Improve quality of life during and after treatment

Minimize hospitalizations!!

Meet patient-generated goals
Tumor-Associated Vasogenic Edema
Steroid Dose Equivalents
can be given intravenously or orally

<table>
<thead>
<tr>
<th>DRUG</th>
<th>Dose equivalent</th>
<th>Biological half-life, hrs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>cortisone</td>
<td>20mg</td>
<td></td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>0.75</td>
<td>36-72</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>20</td>
<td>8-12</td>
</tr>
<tr>
<td>Prednisone</td>
<td>5</td>
<td>12-36</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>4</td>
<td>12-36</td>
</tr>
</tbody>
</table>

How to decide which one to take?
Are there alternatives? VEGF?
How many times per day?
Complications of Corticosteroids:
not always related to dose but try to take the smallest
dose necessary to control symptoms

**Common**
- Myopathy
- Weight gain/edema
- Behavioral changes
- Insomnia
- Diabetes
- Tremor
- Visual blurring
- Reduced taste and smell
- Osteoporosis-calcium/vitamin D kyphoplasty/vertebroplasty

**Uncommon**
- Psychosis/hallucinations
- Hiccups
- Dementia
- Seizures
- Epidural lipomatosis
- Avascular necrosis hips
- Allergy suppression
- RPLS/PRES??
- GASTRIC irritation
- INFECTIONS a) Shingles (herpes zoster) b) pneumocystis jiroveci pneumonia c) PML

Prevention:  a) Shingrix b) Bactrim or atovaquone  c) vigilance and minimizing steroids
- DEPENDENCE
Behavioral Changes

• Agitation - Is the person also taking levetiracetam?
• Insomnia - take largest dose early in day - if taking dexamethasone, take 2nd dose in early afternoon – it will last all day
• Psychosis – not dose-related
• Memory impairment
Myopathy

• 10-20% of patients with > 2wks dexamethasone
• 2/3’s of patients developed myopathy during 9th-12th week of steroids
• Respiratory function decline in some
• Lower risk with enzyme-inducing anti-epileptic drugs
• Nonfluorinated glucocorticoid substitution for those who remain steroid dependent– translation: usually choose dexamethasone
• What can you do? Physical activity, physical therapy!
Adrenal Insufficiency
When the body still needs steroids (even if the tumor does not)

• Every physician has a favored withdrawal regimen
• Marked inter-individual variability in hypothalamic-pituitary axis suppression: 1-2% pts develop Adrenal Insufficiency (1-10 months)
• Symptoms nonspecific: fatigue*, somnolence, abdominal pain, nausea, joint pain, anorexia, weight loss, mood change, cold, tremor, confusion
• Blood test: check 8 am cortisol (then perhaps other tests) OR...
• Treat AI with hydrocortisone: 20 mg in am and 10 mg in afternoon--?? Stress doses
# Emergencies in Brain Tumor Patients

<table>
<thead>
<tr>
<th>Clinical Syndrome</th>
<th>Emergent Diagnostic Tests</th>
<th>Emergent Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Status Epilepticus</strong></td>
<td>EEG</td>
<td>Terminate seizures with an anti-convulsant and increase or add AED</td>
</tr>
<tr>
<td><strong>Deep Venous Thrombosis</strong></td>
<td>Lower Extremity Ultrasound</td>
<td>LMWH Vena Cava Filter only if contraindications to anti-coagulation</td>
</tr>
<tr>
<td><strong>Pulmonary Embolism</strong></td>
<td>CT Angiogram Chest</td>
<td>LMWH IV Heparin if medically unstable Vena Cava Filter if contraindications to anti-coagulation</td>
</tr>
<tr>
<td><strong>Cerebral Venous Thrombosis</strong></td>
<td>MR Venogram</td>
<td>Anti-coagulation</td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td>MRI with DWI</td>
<td>Risk Factor Modification Stop Bevacizumab IV TPA relatively contraindicated</td>
</tr>
<tr>
<td><strong>Intracranial Hemorrhage</strong></td>
<td>CT head without contrast</td>
<td>Stop or reverse anti-coagulation Stop bevacizumab Reduce blood pressure</td>
</tr>
<tr>
<td><strong>Pneumocystis Pneumonia</strong></td>
<td>Chest X-ray, cultures</td>
<td>Trimethoprim Sulfamethoxazole</td>
</tr>
<tr>
<td><strong>Cerebral Abscess</strong></td>
<td>MRI with DWI and ADC</td>
<td>Surgical Aspiration and broad spectrum IV antibiotics</td>
</tr>
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</table>

Legend. EEG= electroencephalography, AED= anti-epileptic drug, LMWH= low molecular weight heparin, DWI= diffusion weighted images, TPA= tissue plasminogen activator ADC= apparent diffusion coefficient
• Brain tumors produce a hypercoagulable state
  Glioblastoma is highest risk group;
  Meningiomas also high – equal to pancreatic cancer

• Cancer-related VTE better treated with heparinoids (enoxaparin and others) than with warfarin

• Multimodality preventive approach: compression stockings, pneumatic boots, heparinoid injections one day after surgery

• Role of oral agents (dabigatran, rivaroxaban, apixaban) not established
Venous thromboembolism (VTE)

- Gliomas:
  - 20-30% incidence, highest in glioblastoma
  - Glial tissues are rich in tissue factor
  - Risk factors: age > 75, paralyzed limb, blood type
- Meningiomas: 5% risk after surgery

- Prevention of VTE:
  - PRODIGE study terminated early (dalteparin injections)
    - Trend toward less clotting but increase in intracranial bleeding
  - Routine prophylaxis not usually continued outside hospital

*courtesy Dr Scott Plotkin
Treatment of Venous Thromboembolism (blood clots) in Brain Tumor Patients

Diagnosis (Doppler ultrasound of legs, CT chest, D-dimer)

- Brain operation within one week?—check with the surgeon!
- High-risk tumor type? (melanoma, choriocarcinoma, renal cell)
- Hemorrhage seen on CT or MRI scan?
- Anticoagulation contraindication? (impending surgery, liver disease, ataxia, platelet count <50,000))

Yes

IVC filter

No

Noncontrast Head CT

- No acute blood
  - IV heparin
    - Tolerated? (no HIT, no bleed)
      - Yes
        - Lifelong anticoagulation: LMWH or warfarin
      - No
        - IVC filter
  - Acute blood
    - IVC filter

KEY: LMWH= low molecular weight heparinoid  HIT heparin-induced thrombocytopenia  IVC inferior vena cava
# Prevention and Treatment of Infectious Complications in Brain Tumors

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage</th>
<th>Precautions</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PJP Prophylaxis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TMP-SMX</strong></td>
<td>1 DS (160/800) tablet daily or 1 SS (80/400) tablet daily or 1 DS (160/800) tablet three times per week</td>
<td>Avoid in patients with Sulfur allergy Delays MTX clearance</td>
<td>Thrombocytopenia, Rash, GI distress, transaminitis</td>
</tr>
<tr>
<td><strong>Dapsone</strong></td>
<td>50 mg twice daily or 100 mg daily</td>
<td>Check for G6PD Deficiency</td>
<td>Fever, rash, methemoglobinemia, Hemolytic Anemia</td>
</tr>
<tr>
<td><strong>Atovaquone</strong></td>
<td>1500 mg daily with food</td>
<td></td>
<td>Fever, rash, diarrhea</td>
</tr>
<tr>
<td><strong>Inhaled Pentamidine</strong></td>
<td>300 mg monthly</td>
<td>Avoid in patients with Asthma</td>
<td>Bronchospasm, cough, wheezing</td>
</tr>
<tr>
<td><strong>Treatment of Oral Candida (7 to 14 days)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clotrimazole Troches</td>
<td>10 mg troche five times a day</td>
<td></td>
<td>GI upset</td>
</tr>
<tr>
<td>Nystatin Swish and Swallow</td>
<td>400,00 to 600,000 units four times a day</td>
<td>Non-compliance in many patients due to taste</td>
<td>Sucrose in formulation can contribute to dental caries</td>
</tr>
<tr>
<td>Miconazole adhesive tablets</td>
<td>50 mg once a day</td>
<td>Tablet applied to a mucosal surface</td>
<td></td>
</tr>
<tr>
<td>Fluconazole (2nd line)</td>
<td>100 to 200mg daily for</td>
<td></td>
<td>Prolonged use can lead to transaminitis</td>
</tr>
</tbody>
</table>

Legend: TMP-SMX= trimethoprim-sulfamethoxazole, DS= double strength, SS= single strength, MTX= methotrexate, GI= gastrointestinal, mg= milligram, G6PD= glucose-6-phosphate dehydrogenase.
Fatigue and mood changes are very common in brain tumor patients

• Fatigue occurs in up to 80% of patients during radiation therapy
  VEGF inhibitors like bevacizumab may worsen fatigue
• What can you recommend?
  Regular sleep, corticosteroids earlier in the day, exercise
  Be careful of most sleep medications for cognitive effects
• Medicines: Methylphenidate, Modafinil, Armodafinil

• Treat depression:
  Change anti-epileptic drug from levetiracetam (lamotrigine good)
  No optimal antidepressant, but avoid bupropion → seizure risk
Cognitive Dysfunction

• Direct effects of tumor— even preoperatively as informed consent is given....
• Radiation therapy
• Some chemotherapy
• What can you do?    Detailed neuropsychological testing
    Have surrogate to aid with decision-making
    Treat fatigue and depression
    Check 8 am cortisol, thyroid function and B12

Neuroprotection:

    Randomized trial of memantine in patients with brain metastases receiving radiation therapy— slight improvement in delayed recall in treated patients.

    Possible mild benefit of donepezil
Putting it All Together During Treatment
The Standard of Care: temozolomide and radiation therapy

Opportunities to Avoid Problems: PJP, PPD, no AED unless seizures occur
flu/pneumovax vaccine, be aware of blood clot symptoms and signs,
calcium and vitamin D supplements, Hepatitis B screen, treat mood and
fatigue
What is Palliative Care? The old model

Disease-Directed Therapies

Disease-directed therapies

Diagnosis  Palliative Care  Death and Bereavement

This and subsequent slide courtesy of Dr. Matthew Mendlik
Palliative Care: the current model -- from the beginning, attention to symptoms!!

Examples of Palliative Interventions:
Bowel motility agents for constipation
Compounding suppository formulations of most anti-epileptic drugs
Nausea treated, sometimes by increasing steroids
Decisions about goals-of-care choices
Are symptoms in neuro-oncology different?

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>High Grade Glioma</th>
<th>General Cancer - last 2 weeks of life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>NR</td>
<td>88%</td>
</tr>
<tr>
<td>Weight loss</td>
<td>NR</td>
<td>86%</td>
</tr>
<tr>
<td>Appetite loss</td>
<td>NR</td>
<td>56%</td>
</tr>
<tr>
<td><strong>Neurological symptoms</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drowsiness</td>
<td>44 – 90%</td>
<td>38%</td>
</tr>
<tr>
<td>Poor Communication</td>
<td>64 – 90%</td>
<td>NR</td>
</tr>
<tr>
<td>Speech Difficulties</td>
<td>29 – 64%</td>
<td>NR</td>
</tr>
<tr>
<td>Focal Deficits</td>
<td>51 – 62%</td>
<td>NR</td>
</tr>
<tr>
<td>Poor Mobility</td>
<td>77%</td>
<td>NR</td>
</tr>
<tr>
<td>Weakness</td>
<td>17 – 25%</td>
<td>74%</td>
</tr>
<tr>
<td>Seizures</td>
<td>10 – 56%</td>
<td>NR</td>
</tr>
</tbody>
</table>

1 Walbert T. and Khan M., End of life symptoms in high grade glioma.  
2 Reunissen S. et al., J Pain Symptom Manage 2007
Late Toxicity from Radiation and/or Chemotherapy

2nd Tumors (meningioma)

Episodes of transient focal dysfunction – rule out seizures, SMART/ALERT

Hydrocephalus:
Cognitive decline, gait
Urinary incontinence
May need shunt

Cerebral microbleeds

Diffuse leukoencephalopathy
reduced neurogenesis, vascular changes
Impaired learning, short-term memory, executive function, attention concentration
The treatment is over!
But we need to be vigilant

• Long-term effects (see checklist): how can we minimize?
• Maintain cardiovascular and bone health
  attention to vascular risk factors
  vitamin D, exercise
  minimize medications, BUT
  treat anxiety, depression
Clinical Checklist for Brain Tumor Survivor Evaluation

**Consequences of anti-epileptic drugs, chemotherapy, and corticosteroids**

- Osteoporosis
- Avascular necrosis (hip, knee)
- Impaired fertility
- Posterior reversible encephalopathy syndrome (PRES)
- Eyes: cataracts, dry eye
- Infections: zoster, pneumocystis, PML
- Secondary neoplasms: AML, melanoma, basal cell carcinoma
- Weight gain, metabolic syndrome
- Cognitive symptoms, sometimes called Chemobrain

**Consequences of radiation therapy**

- Stroke (increased cardiovascular risk, **metabolic syndrome**)
- Hypothalamic/pituitary dysfunction- growth hormone deficiency
- Communicating hydrocephalus
- Osteonecrosis of jaw
- Radiation-induced tumors (astrocytoma, meningioma, sarcoma, thyroid, skin, AML)
- Hearing loss
- Cavernous angiomas (seizure, hemorrhage in brain or cord)
- Superficial siderosis- hearing loss, ataxia, myelopathy
- Prolonged stroke-like migraines (SMART syndrome)
- Vascular disease- microangiopathy, pseudoaneurysms, large vessel, Moya-Moya
- Cognitive decline
- Carotid atherosclerosis with neck XRT
- Melatonin deficiency (craniopharyngioma)
- Cervical disc disease (posterior fossa XRT to paraspinous muscles)
The Neuro-Oncology Team

- Surgeon
- Medical Oncologist
- Primary Care Nurses, Nurse Practitioners
- Social Service Psychology, Navigators
- Radiation Oncologist
- Neurologist, Neuro-oncologist
- Research Coordinator, Pathologist, Radiologist, Pharmacist
- Physical Therapy, Rehabilitation Palliative Care