PALLIATIVE CARE IN BRAIN TUMORS

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Overview

- Seizure prophylaxis and anticonvulsant use
- Treatment of peritumoral edema
- Steroid-induced complications
- Fatigue/Neuro-cognitive
- DVT/PE and anticoagulation
- Radiation necrosis
- Pain/Headaches

WHO Palliative Care in Cancer Initiative

- provides relief from pain and other distressing symptoms;
- affirms life and regards dying as a normal process;
- intends neither to hasten or postpone death;
- integrates the psychological and spiritual aspects of patient care;
- offers a support system to help patients live as actively as possible until death;
- offers a support system to help the family cope during the patients illness and in their own bereavement;
- uses a team approach to address the needs of patients and their families, including bereavement counselling, if indicated;
- will enhance quality of life, and may also positively influence the course of illness;
- is applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life, such as chemotherapy or radiation therapy, and includes those investigations needed to better understand and manage distressing clinical complications.

http://www.who.int/cancer/palliative/en/

Palliative Care

- Should be engaged at the beginning of the disease, not wait until end of life
- focus on symptom managements and psychosocial support
- Early involvement can improve symptom management and end-of-life decisions

SEIZURES IN BRAIN TUMORS

UCLA Brain Tumor Center

Seizure in Brain Tumors

- 70% low grades have seizures, vs 29-49% in GBM[1]
- Presenting symptom ~40%
  - Half are not controlled prior to surgery
  - Seizures have an impact on QOL and function of patient
- Treatment shown to decrease # seizures
  - Surgical debulking substantially increases seizure free percentage
  - radiotherapy and chemotherapy may improve seizure control in retrospective data

1. Van Breemen et al, Lancet Neurol, 2007

Seizure Prophylaxis

- Patients with seizures
  - Should be treated with standard AED
  - Preference for cytochrome P450-enzyme non-EIAED
  - EEG usually not necessary
- Patients likely to have seizures or who would be devastated by seizures?
  - Mets that bleed: melanoma, choriocarcinoma, renal
  - Mets to temporal lobe
  - Patients with large tumors and acute to subacute neurologic symptoms
  - tumors to temporal lobe or insula

Choice of Anti-epileptic Medication

- No data suggesting one medication better than another for brain tumors
- Limit cognitive side effects
- Multiple purposes: e.g. seizure treatment & mood stabilization or pain control
- Drug interactions
  - With chemotherapeutic or molecular targeted agents
  - With dexamethasone

Phase I/II Study of Imatinib Mesylate for Recurrent Malignant Gliomas

- EIAD significantly reduces concentration of cancer therapeutic agents
- Increasing dosages of the agent cannot compensate for the interaction

EIAEDs and Non-EIAEDs

EIAEDs

Carbamazepine

Oxcarbazepine

Phenytoin

Fosphenytoin

Phenobarbital

Primidone

N-EIAEDs

Valproic acid

Gabapentin

Lamotrigine

Topiramate

Tiagabine

Zonisamide

Levetiracetam

Clonazepam

Clonozam

Pregabalin

Lacosamide

EORTC/NCIC Temozolomide Trial

- 175 patients (30.5%) were AED free, 277 (48.3%) were receiving EIAEDs, and 135 (23.4%) were receiving non-EIAEDs
- 97 patients receiving valproic acid alone had increased survival from treatment with RT and TMZ
  - Valproic acid median survival: 17.3 mos
  - EIAED only median survival: 14.4 mos
  - No AED median survival: 14.0 mos
- Patients receiving valproic acid only had more grade 3/4 thrombocytopenia and leukopenia

Weller M, et al. Neurology. 2011;77:1156-1164.

EORTC/NCIC Temozolomide Trial

AED Status	HR (95% CI)
No AED	0.64 (0.46-0.89)
VPA only	0.41 (0.26-0.65)
EIAED only	0.69 (0.53-0.89)

Weller M, et al. Neurology. 2011;77:1156-1164.

Prophylactic Anticonvulsants

PRACTICE PARAMETER: ANTICONVULSANT PROPHYLAXIS IN PATIENTS WITH NEWLY DIAGNOSED BRAIN TUMORS

Report of the Quality Standards Subcommittee of the American Academy of Neurology

M.J. Glantz, MD; B.F. Cole, PhD; P.A. Forsyth, MD; L.D. Recht, MD; P.Y. Wen, MD; M.C. Chamberlain, MD; S.A. Grossman MD; and J.G. Cairncross, MD

- No definite evidence that patients who have not had seizures benefit from prophylactic AED
- Recommend tapering AED 1 wk after surgery
- Current ongoing trial evaluating need for AED prophylaxis at all

Glantz MJ, et al. Neurology. 2000;54:1886-1893.

EDEMA CONTROL

Peritumoral Edema

- Glucocorticoids preferred
  - Dexamethasone lacks mineralocorticoid effects
- Twice daily dosing adequate
  - Dexamethasone t½ : 36-54h
  - Avoid late night dosing to prevent insomnia
- Get the desired effect quickly and then use as little as possible
  - No standardized regimen, starting dosage based on individual patient – size of tumor, location, amount of edema, severity of symptoms

Neurologic Complications of Corticosteroids

- Common
  - Myopathy
  - Behavioral change
  - Visual blurring
  - Tremor
  - Insomnia
  - Reduced taste and olfaction
  - Cerebral atrophy
  - Decrease immune system
  - Increase glucose
  - Adrenal insufficiency
- Uncommon
  - Psychosis
  - Hallucinations
  - Hiccups
  - Dementia
  - Seizures
  - Dependence
  - Epidural lipomatosis
  - Steroid psychosis
  - GI bleed

Pneumocystis Jerovecii (Carinii) Pneumonia

- High risk of PCP pneumonia in brain tumor patients
- From chronic corticosteroid use
- Or from high dose or daily chemotherapy
  - High dose methotrexate
  - Temozolomide
    - "Stupp regimen" – 79% grade III lymphopenia; 2 patients developed PCP and protocol amended to start PCP prophylaxis on all patients
    - Recommended to start PCP prophylaxis on all patients receiving daily Temozolomide during concurrent RT
    - Also start prophylaxis if lymphocytes <500

Mahindra AK, et al. J Neurooncol. 2003;63:263-270.
Stupp et al, JCO, 2002
DeVos FY et al, Crit Rev Onc Hematol 2013

Osteoporosis and Compression Fractures

- From chronic steroid use
- Metabolic effects of corticosteroids on bones
- Osteoporosis leading to fractures if spine or hip
  - Avascular necrosis of the hip
  - Compression fractures of spine

Osteoporosis

- Patients receiving chronic corticosteroid therapy should consider
  - Calcium supplements with vitamin D
  - Bisphosphonates such as etidronate, alendronate, risedronate, and zoledronate
- Kyphoplasty: unclear benefit for compression fractures[1]
  - 2 negative trials have been reported but several cases of empiric symptomatic relief

1. Muijs SP, et al. J Bone Joint Surg Br. 2011;93:1149-1153.

Novel Treatments for Peritumoral Edema

- COX-2 inhibitors[1]
- Corticorelin acetate (corticotrophin-releasing factor)[2,3]
- VEGF inhibitors (eg, bevacizumab, aflibercept)
- VEGFR inhibitors

1. Portnow J, et al. Neuro Oncol. 2002;4:22-25. 2. Shapiro WR, et al. ASCO 2009. Abstract 2080.
3. Recht LD, et al. ASCO 2010. Abstract 2078.

Cediranib: VEGFR Inhibitor

Percent Change of Lowest Corticosteroid Dose From Baseline

Friedman HS, et al. J Clin Oncol. 2009;27:4733-4740.

Bevacizumab

- Patients in both arms, Avastin only and Avastin + Irinotecan, were able to reduce Corticosteroids doe from baseline
  - Only look at progression-free patients

Friedman HS, et al. J Clin Oncol. 2009;27:4733-4740.

FATIGUE

Fatigue and Neurocognitive issues

- Can worsen neurocognition
- Treatment trials – no clear evidence for improvements
  - Abulia, inattention (methylphenidate)[1]
  - Cognitive Fatigue (modafinil, armodafinil, methylphenidate)
    - No significant improvement in randomized trials to improve fatigue after irradiation[2,3]
- Related cause - Depression (often underdiagnosed)
  - UCLA Neuro-Oncology screening found 46% of patients with elevated depression[4]

1. Myers CA, et al. J Clin Oncol. 1998;16:2522-2527. 2. Shaw EG, et al. JCO, 2013. 3. Lee EQ, et al, JCO 2014. 4. Banerjee et al, SNO Abstract, 2014.

NEUROCOGNITIVE ISSUES

Cognitive Difficulties

- Assessment
  - Neuropsychological assessments to determine
    - Cognitive strengths and weaknesses
    - Extent of impairments
    - Potential diagnositic etiologies/contributing factors
    - Recommendations for cognitive rehab
- Contributing factors
  - Fatigue or Lack of Sleep
  - Cancer treatments
  - Mood/Depression

Adapted from Dr. Pia Banerjee, Brain Tumor Patient Conference, 2015

Cognitive Difficulties - Treatment

- Pharmacologic – no significant improvements in memory
  - Donepezil (Rapp SR. et al, JCO, 2015)
    - randomized trial for patients 6 mos post-RT
    - No significant improvement in overall cognitive function
    - Seems to improve subset of patients who already had severe cognitive problems prior to RT
  - Memantine (RTOG 0614, Brown PD et al, NeuroOnc 2013)
    - Randomized trials of patients with brain Mets undergoing WBRT
    - no significant difference in cognitive function
    - However, Memantine treatment seems to slow decline in memory, executive function

Cognitive Difficulties - Treatment

- Cognitive Rehab
  - Restorative – to bring back old skills
  - Reorganization – develop new ways to substitute for what has been lost
  - Compensatory – use patient's strengths and environmental support to find new approaches
    - need to target individual's needs, more often used

Adapted from Dr. Pia Banerjee, Brain Tumor Patient Conference, 2015

1. Shaw EG, et al. J Clin Oncol. 2006;24:1415-1420

VENOUS THROMBOSIS

Venous Thromboembolic Disease

- Highest incidence in brain cancers among all cancers, comparable to pancreatic and gynecologic malignancies
- Majority occur in postoperative period
- > 40% occur outside postoperative period
- 17% at 6 mos, ~21% rate at 12 mos; 32% at 24 mos
- Risk factors for VTE: higher age, prior DVT, leg paralysis, obesity, anti-VEGF therapy, hormonal therapy, venous access device, recurrent disease

Gerber DE, et al. J Clin Oncol. 2005;24:1310-1318.
Schiff D, et al, Neurooncology 2015.

Complications of Inferior Vena Cava Filter

- 42 brain tumor patients who had IVC filters place
  - 12% experienced recurrent PE
  - 57% developed either IVC or filter thrombosis, recurrent DVT, or postphlebitic syndrome
- 42 patients with brain metastases and VTE who received anticoagulation
  - 3 (7%) experienced cerebral hemorrhage, 2 with supratherapeutic anticoagulation
  - 10 patients who received an IVC filter, 4 (40%) developed recurrent VTE requiring anticoagulation

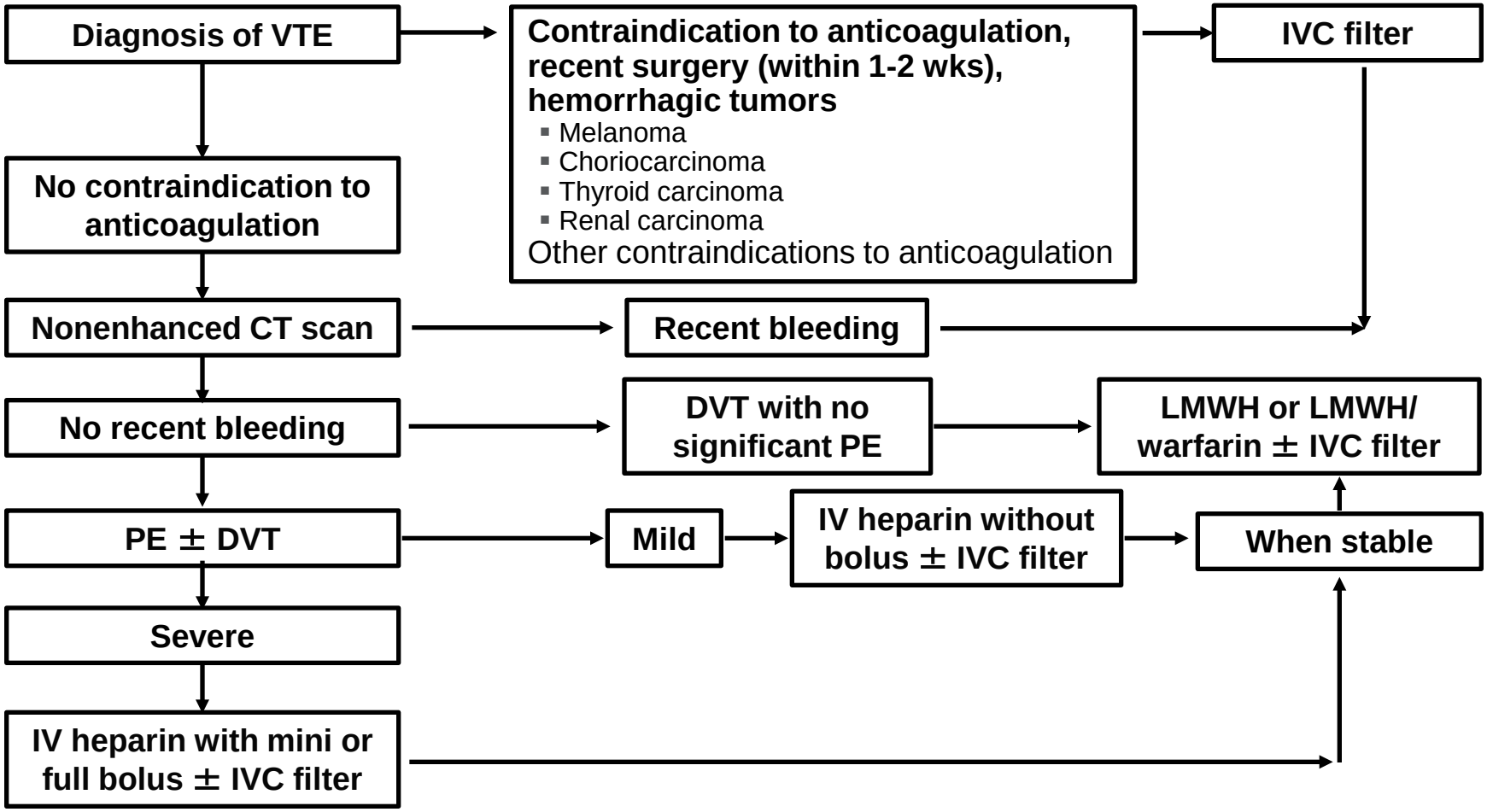
1. Levin JM, et al. Neurology. 1993;43:1111-1114. 2. Schiff D, et al. Cancer 1994;73:493-498.

Risks of Anticoagulation

- in Malignant Glioma patients[1,2]
  - 2/103 (1.9%) with VTE, who were anticoaglated, experienced ICH
  - 6/272 (2.2%) with VTE had spontaneous hemorrhage
  - In another series, 0/22 experienced ICH
- In patients with melanoma, no difference in ICH between patients receiving anticoagulation vs those without[3]

1. Ruff RL, et al. Ann Neurol. 1983;13:334-336. 2. Choucair AK, et al. J Neurosurg. 1987;66:357-358.
3. Alvarado et al, Melanoma Res, 2012

Algorithm for VTE Treatment in Patients With Brain Tumors



Wen PY, et al. J Neurooncol. 2006;80:313-3332.

Safety of Anticoagulation Use and Bevacizumab in Patients With Glioma

- N = 21 patients treated for mean of 72 days
- No lobar hemorrhages
- 3 small parenchymal hemorrhages
  - 1 symptomatic
  - 2 petechial hemorrhages

Safety of Concurrent Bevacizumab and Anticoagulation in High-Grade Gliomas

- 64 patients with glioma treated with bevacizumab and anticoagulation
- 7 (10.9%) experienced intracranial hemorrhage
  - Grade 4: 2 (3.1%)
  - Grade 1: 5 (7.8%)
- Among 218 patients who did not receive anticoagulants, there were 2 (0.9%) serious hemorrhages (both grade 4 intracranial hemorrhages)

Norden AD, et al. J Neurooncol. 2011;[E-pub ahead of print].

LMWH (Dalteparin) ± Coumarin for VTE Prophylaxis: Risk of Recurrence

- Cancer patients with VTE randomized to dalteparin ± coumarin derivative
- 6-mo VTE rates
  - Dalteparin: 27/336 (9%)
  - Coumarin: 53/336 (17%)
  - HR: 0.48; *P* = .002
  - No difference in bleeding or death

Lee AY, et al. N Engl J Med. 2003:349:146-153.

Prophylactic Anticoagulation

- Role of long-term prophylactic anticoagulation unknown
- PRODIGE randomized phase III trial of daily dalteparin vs placebo in patients with newly diagnosed malignant glioma
  - Terminated prematurely
  - Dalteparin associated with trend toward decreased VTE and increased bleeding

Perry JR, et al. J Thromb Haemost. 2010;8:1959-1965.

RADIATION NECROSIS

Complications of Radiation Therapy on the Nervous System

- Still difficult to diagnose, but possibly 20-30% of primary brain tumors with radiation necrosis post-RT
- Direct effects on neural structures within radiation portal
  - Acute reaction (hrs or days)
  - Early delayed reaction (2 wks to 4 mos)
  - Late delayed reaction (4 mos to several yrs)
- Indirect effects
  - Vascular injury (cerebral infarction and hemorrhages)
  - Secondary neoplasms
  - Endocrinopathies

Treatment of Radiation Necrosis

- Corticosteroids
- Surgery
- Pentoxifylline?
- Anticoagulation?
- Hyperbaric oxygen?

Radiation Necrosis

- Retrospective review of 8 pts treated with Bevacizumab for brain tumors with radiation necrosis
  - Dramatic decrease in edema and necrosis
  - Treated at 5 mg/kg/2 weeks or 7.5 mg/kg/3 weeks

Gonzalez J, et al. Int J Radiat Oncol Biol Phys. 2007;67:323-326.

Bevacizumab vs Placebo in Patients With Radiation Necrosis

- N = 14 patients with radiation necrosis randomized placebo or bevacizumab (7.5 mg/kg every 3 wks)
- Response
  - 0/7 placebo
  - 7/7 bevacizumab

Levin VA, et al. Int J Radiat Oncol Biol Phys. 2011;79:1487-1495.

Radiation Necrosis and Bevacizumab

- Not FDA approved for treatment of radiation necrosis

PAIN MANAGEMENT

UCLA Brain Tumor Center

WHO Pain Ladder

http://www.who.int/cancer/palliative/painladder/en/

Headaches

- Most common type of pain in brain tumor patients
  - Usually lacks other systemic pain
  - Equally prevalent in primary brain tumors or mets
- In a study of 206 patients with brain tumors[1]
  - Nearly half has headaches
  - More likely in those who had headaches prior to diagnosis
  - Also depends on location: midline tumors, causing midlines shift or raised ICP
  - More common in GBM or secreting pituitary adenomas vs low grade gliomas

1. Valentinis et al, Cephalagia, 2010.

Headaches

- Types of headaches
  - A study of 111 brain tumors patients found classic presenting symptoms in only 17%[1]
    - Classic brain tumor headaches = severe early morning headaches associated with nausea and vomiting
    - Can have tension types, migraines, or other headaches
- Treatments
  - Corticosteroids if headaches from edema
  - Migraine types can be treated with migraine medications – especially if have history of migraines
  - Non-opioids or opioids for severe headaches

1. Forsyth and Posner JB, Neurology, 1993.

Headaches

- Patients can develop chronic daily headaches even if tumors under control
  - Consider Medications Overuse
  - Underlying factors – Mood
  - Chronic pain management
- May have sudden relapse of headaches
  - Sign of possible tumor relapse

1. Forsyth and Posner JB, Neurology, 1993.

Conclusion

- Palliative care for brain tumor patients should start with diagnosis
- Require multidisciplinary involvement in care of brain tumor patients
- Supportive care and effective management/prevention of complications can prevent further impairment of quality of life.