Management of Medical and Neurologic Complications in Cancer Patients

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DISCLOSURES

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Outline

• Anti-Epileptic Drugs
• Peritumoral edema
• Venous Thromboembolic Disease
• Miscellaneous
  – Fatigue
  – Cognitive difficulties
## Incidence And Risk Factors Of Epilepsy Across Brain Tumor Types

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Approximate incidence of seizures</th>
<th>Risk factor for seizures</th>
<th>References</th>
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</thead>
<tbody>
<tr>
<td>Glioneuronal tumors</td>
<td>70–80%</td>
<td>Frontotemporal, insular</td>
<td>Aronica et al. (2001); Luyken et al. (2003); Southwell et al. (2012)</td>
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<tr>
<td>Low-grade gliomas</td>
<td>60–75%</td>
<td>Frontotemporal, insular, superficial</td>
<td>Chang et al. (2008a); Pignatti et al. (2002); Recht and Glantz (2008); Lee et al. (2010); You et al. (2012); Iuchi et al. (2015)</td>
</tr>
<tr>
<td>High-grade gliomas</td>
<td>25–60%</td>
<td>WHO grade III, temporal lobe, superficial</td>
<td>Sheth (2002); van Bremmen et al. (2007); Jacoby et al. (2008); Chaichana et al. (2009b); Sizoo et al. (2010)</td>
</tr>
<tr>
<td>Meningiomas</td>
<td>20–50%</td>
<td>Peritumoral edema</td>
<td>Yao (1994); Chow et al. (1995); Lieu and Howng (2000); Oberndorfer et al. (2002)</td>
</tr>
<tr>
<td>Metastases</td>
<td>20–35%</td>
<td>Melanoma, lung cancer</td>
<td>Oberndorfer et al. (2002); Lynam et al. (2007); Avila (2013)</td>
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</table>

WHO, World Health Organization.
Preoperative seizures observed in 18%–34% of IDH1 wild-type (IDH1wt) patients and in 59%–74% of IDH1mut patients (p < 0.001)

Multivariable analysis showed that IDH1mut was an independent correlate with seizures (odds ratio 2.5, 95% confidence interval 1.6–3.9, p < 0.001)

D2HG product of IDH1mut may increase neuronal activity by mimicking the activity of glutamate on the NMDA receptor

D2HG increased the firing rate of cultured rat cortical neurons 4- to 6-fold, but was completely blocked by AP5 (NMDA inhibitor)
Patients with seizures

• Should be treated with standard AED
• Preference for non-cytochrome P450-enzyme inducing AED
• EEG usually not necessary
Results of 4 phase III trials: AVAglio, CENTRIC, CORE, RTOG0825

VPA use at start of chemoradiotherapy was not associated with improved PFS or OS compared with other patients pooled (PFS: hazard ratio [HR], 0.91; 95% CI, 0.77 to 1.07; P = .241; OS: HR, 0.96; 95% CI, 0.80 to 1.15; P = .633)

No association with improved outcomes was observed for levetiracetam use

No definite evidence that patients who have not had seizures benefit from prophylactic AED

Preferable to Use non-enzyme inducing AED
Recommendations for Anticonvulsant Therapy for Patients with Gliomas

• **Patients with Seizures**
  – Anticonvulsants

• **Patients without Seizures**
  – No definite evidence of benefit after 1<sup>st</sup> or 2<sup>nd</sup> week post-op
  – Fairly high risk of further seizures

• **Prospective randomized study needed**
Peritumoral Edema

• Glucocorticoids preferred
• Once or twice daily dosing adequate
• Use as little as possible
• Anti-VEGF therapies has reduced need for steroids
Glucocorticoids induce expression:
1) Tight junction proteins **occludin** and **claudin-5**
2) Adherens junction protein vascular endothelium cadherin (**VE-cadherin**)

Courtesy of Michael White
Neurologic Complications of Corticosteroids

- **Common**
  - Myopathy
  - Behavioral changes
  - Visual blurring
  - Tremor
  - Insomnia
  - Reduced taste and olfaction
  - Cerebral atrophy

- **Uncommon**
  - Psychosis
  - Hallucinations
  - Hiccups
  - Dementia
  - Seizures
  - Dependence
  - Epidural lipomatosis
Corticosteroids compromise survival in glioblastoma


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Brain Advance Access published March 28, 2016

doi:10.1093/brain/aww046
Letter: When Less is More: Dexamethasone Dosing for Brain Tumors

To the Editor:

We are writing to highlight the discrepancy in dosing schedules for corticosteroids used to treat peritumoral edema between the neurosurgical community and the neuro-oncology community and suggest that it may be time to re-evaluate the dosing of dexamethasone for brain tumors.

Administering corticosteroids every 6 h frequently can result in poor sleep due to medication-related effects or medication administration itself, contributing to increased daytime fatigue. In a population where preserving the quality of life is paramount, and in the absence of evidence to justify more frequent dosing, we hope the neurosurgical community will join the neuro-oncology community and consider changing its practice to once or twice a day dosing of dexamethasone for brain tumor patients.
Venous Thromboembolic Disease

- Common
- Among the highest incidence among cancers, comparable to pancreatic and GYN malignancies
- Majority in post-operative period; > 40% outside post-operative period
- Overall risk @ 8% - 30%
  - Perry Neuro-Oncology 2012; Sep;14 Suppl 4:iv73-80
  - Brandes et al Eur J Cancer. 1997;33:1592–1596
  - Marras et al Cancer. 2000;89:640–646
# Risk Factors For Venous Thromboembolism in Brain Tumors

| Patient-related risk factors | • Older age  
|                           | • Obesity  
|                           | • Dependent functional status (i.e., patients who require assistance from another person for activities of daily living)  
|                           | • Leg paresis  
| Treatment-related risk factors | • Surgery  
|                           | • Tumor biopsy  
|                           | • Subtotal tumor resection  
|                           | • Use of corticosteroids  
|                           | • Anti-VEGF therapy  
| Tumor-related risk factors | • Glioblastoma subtype (as compared with lower-grade gliomas)  
|                           | • Intratumoral thrombosis  
|                           | • IDH1 wild-type status  
|                           | • Podoplanin expression  
| Laboratory parameters and hemostatic biomarkers | • High white blood cell count  
|                           | • Low platelet count (in contrast to solid tumors)  
|                           | • High soluble P-selectin levels  
|                           | • Elevated coagulation factor VIII activity  
|                           | • Increased D-dimer levels  

Abbreviation: IDH1, isocitrate dehydrogenase 1; VEGF, vascular endothelial growth factor; VTE, venous thromboembolism.
Safety of Concurrent Bevacizumab Therapy and Anticoagulation in High-Grade Glioma Patients

- 64/282 HGG treated with bevacizumab and anticoagulation
- 7 (10.9%) were intracranial
  - 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)
- Serious hemorrhage rate was higher in patients who received anticoagulants (p=0.025), but the rate is low
Lee et al (NEJM 2003; 349:146-153)

- Cancer patients with VTE randomized to coumadin or dalteparin
- After 6 months
  - 27/336 dalteparin had VTE (9%)
  - 53/336 coumadin pt had VTE (17%)
    - (P=0.002)
- No difference in bleeding or death

Figure 1. Kaplan–Meier Estimates of the Probability of Symptomatic Recurrent Venous Thromboembolism among Patients with Cancer, According to Whether They Received Secondary Prophylaxis with Dalteparin or Oral Anticoagulant Therapy for Acute Venous Thromboembolism.

An event was defined as an objectively verified, symptomatic episode of recurrent deep-vein thrombosis, pulmonary embolism, or both during the six-month study period. The hazard ratio for recurrent thromboembolism in the dalteparin group as compared with the oral-anticoagulant group was 0.48 (95 percent confidence interval, 0.30 to 0.77; P=0.002 by the log-rank test).
Edoxaban for the Treatment of Cancer-Associated Venous Thromboembolism

Gary E. Raskob, Ph.D., Nick van Es, M.D., Peter Verhamme, M.D., Marc Carrier, M.D., Marcello Di Nisio, M.D., David Garcia, M.D., Michael A. Grosso, M.D., Ajay K. Kakkar, M.B., B.S., Michael J. Kovacs, M.D., Michele F. Mercuri, M.D., Guy Meyer, M.D., Annelise Segers, M.D., Minggao Shi, Ph.D., Tzu-Fei Wang, M.D., Erik Yeo, M.D., George Zhang, Ph.D., Jeffrey I. Zwicker, M.D., Jeffrey I. Weitz, M.D., and Harry R. Bülle, M.D., for the Hokusai VTE Cancer Investigators®

A

No. at Risk
Edoxaban 522 480 437 415 395 370 356 340 320 307 281 245 168
Daltreparin 524 488 452 423 389 370 358 348 333 321 282 246 174

B

No. at Risk
Edoxaban 522 484 447 426 404 375 358 343 323 308 282 248 168
Daltreparin 524 497 466 436 409 390 378 356 346 335 298 262 183
Fig 2. Time to venous thromboembolism (VTE) recurrence within 6 months.

Young et al JCO 2018
Retrospective review of 172 pts (42 DOAC and 131 LMWH)

Primary brain tumor cohort (n = 67), the cumulative incidence of any ICH was 0% in patients receiving DOACs vs. 36.8% (95% confidence interval [CI], 22.3–51.3%) in those treated with LMWH, with a major ICH incidence of 18.2% (95% CI, 8.4–31.0)

Brain metastases cohort (n = 105), DOACs did not increase the risk of any ICH relative to enoxaparin, with an incidence of 27.8% (95% CI, 5.5–56.7%) compared with 52.9% (95% CI, 37.4–66.2%). Similarly, DOAC did not increase the incidence of major ICH in brain metastases, with a cumulative incidence 11.1% (95% CI, 0.5–40.6%) vs. 17.8% (95% CI, 10.2–27.2%)

DOACs are not associated with an increased incidence of ICH relative to LMWH in patients with brain metastases or primary brain tumors
Recommendations for Patients With VTE

- IVC filter if hemorrhage on CT or other contraindication for anticoagulation
- Heparin initially for sick patients
- LMWH for stable patients
- ? Long term anticoagulation with LMWH preferable for GBM
- ? Role of oral agents such as apixaban (Factor Xa inhibitor)
A randomized, placebo-controlled pilot trial of armodafinil for fatigue in patients with gliomas undergoing radiotherapy


Patients with grade 2-4 glioma undergoing brain irradiation

RANDOMIZE 1:1

- Armodafinil 150 mg daily
- XRT 50-60 Gy
- Placebo daily

Baseline D 22 D 43 D 56

- Fatigue assessments with the FACIT-F Fatigue Scale, Brief Fatigue Inventory (BFI), and Cancer Fatigue Scale (CFS) at baseline, day 22, day 43, and day 56.

- PRIMARY ENDPOINT: Difference in the 42-day change in FACIT-F fatigue subscale scores between armodafinil group vs. placebo group

- SECONDARY ENDPOINTS: 42-day change in CFS and BFI, safety
• 198 adult brain tumor survivors 6 months after partial- or whole-brain irradiation randomly assigned to receive a single daily dose (5 mg for 6 weeks, 10 mg for 18 weeks) of donepezil or placebo

• Cognitive test battery assessing memory, attention, language, visuomotor, verbal fluency, and executive functions was administered before random assignment and at 12 and 24 weeks. A cognitive composite score (primary outcome) and individual cognitive domains were evaluated
After 24 weeks of treatment, the composite scores did not differ significantly between groups ($P = .48$).

Modest improvements in several cognitive functions, especially among patients who were more cognitively impaired.

Significant differences favoring donepezil were observed for memory (recognition, $P = .027$; discrimination, $P = .007$) and motor speed and dexterity ($P = .016$).
Minimizing neurocognitive decline from WBRT?

- **RTOG 0614:** phase III randomized, placebo-controlled study
- Placebo vs. Memantine 20 mg daily within 3 days of starting WBRT 37.5 Gy and continued for 24 weeks

<table>
<thead>
<tr>
<th>Cognitive domain</th>
<th>Measure</th>
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<tbody>
<tr>
<td>Memory</td>
<td>Hopkins Verbal Learning Test-Revised</td>
</tr>
<tr>
<td>Processing speed</td>
<td>Trail making test Part A</td>
</tr>
<tr>
<td>Executive function</td>
<td>Trail making test Part B, controlled oral word association</td>
</tr>
<tr>
<td>Global function</td>
<td>Mini-mental status examination</td>
</tr>
<tr>
<td>Cognitive function (self-report)</td>
<td>Medical outcomes scale – cognitive function scale</td>
</tr>
<tr>
<td>Quality of life</td>
<td>Fact-Br</td>
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</tbody>
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MRI, Cognitive Assessment and QOL at Baseline, 8, 16, 24 and 52 weeks
Outcomes: RTOG 0614

- Primary endpoint: Reduced the decline in HVLT-R DR by 0.9 (P=.059) at 24 weeks

- 17% reduced relative risk of cognitive decline (p=.01)

- Delayed time to cognitive decline (p=.01)

- Reduced the rate of decline in cognitive, executive, and global function as well as processing speed (p<.01)
Patients with brain metastases received HA-WBRT to 30 Gy in 10 fractions.

Standardized cognitive function and quality-of-life (QOL) assessments were performed.

113 patients accrued, 42 patients were analyzable at 4 months.

Mean relative decline in HVLT-R DR from baseline to 4 months was 7.0% (95% CI, 4.7% to 18.7%), significantly lower in comparison with the historical control (P 0.001). No decline in QOL scores was observed.

Conformal avoidance of the hippocampus during WBRT is associated with preservation of memory and QOL compared with historical series.
Grade 0 indicates no improvement; grade 1, mild improvement; grade 2, moderate improvement; and grade 3, marked improvement.

Exercise Behavior, Functional Capacity, and Survival in Adults With Malignant Recurrent Glioma

Emily Ruden, David A. Reardon, April D. Coan, James E. Herndon II, Whitney E. Hornsby, Miranda West, Diane R. Fels, Annick Desjardins, James J. Vredenburgh, Emily Waner, Allan H. Friedman, Henry S. Friedman, Katherine B. Peters, and Lee W. Jones

Conclusion
Exercise behavior is a strong independent predictor of survival that provides incremental prognostic value to KPS as well as traditional markers of prognosis in malignant recurrent glioma.
• 191 newly diagnosed GBM patients
• Hyperglycemia associated with shorter survival, after controlling for glucocorticoid dose and other confounders
• Effect of intensive management of glucocorticoid-related hyperglycemia on survival deserves additional study

**Association Between Hyperglycemia and Survival in Patients With Newly Diagnosed Glioblastoma**

Rachel L. Derr, Xiaobu Ye, Melissa U. Islas, Serena Desideri, Christopher D. Saudek, and Stuart A. Grossman
References