Evidenced-Based Symptom-Directed Treatments in Neuro-Oncology

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No Relevant Disclosures
Evidenced-Based Advances in Symptom-Directed Treatment

• MODEL: MALIGNANT GLIOMA PATIENTS, HOWEVER THESE TREATMENTS ARE GERMAINE TO MOST CNS TUMORS CARED FOR BY NEUROSURGEONS
• Disease Modeling & Prognostication
• Performance Status
  – Assessment
  – Stratification
  – Optimization
• Toxicity prevention & mitigation
  – Tumor-related
  – Treatment-related
• Manage specific symptoms
  ▪ Surveillance protocols
    ▪ Tumor progression
    ▪ Delayed sequel of treatment (survivorship)
• Only a fraction of Malignant Giomas are “cured” and none are “asymptomatic” across a lifetime
• Thus, an essential part of treatment must include evidenced-based symptom-directed (palliative) treatment
Historical Illness Trajectory in Malignant Gliomas

- Malignant Gliomas historically follow the trajectory of unremitting, progressive neurologic diseases
- Criteria for entering Palliative Care & Hospice programs should follow such diseases, not systemic cancers
- Evidenced-Based symptom-directed treatments are changing this illness trajectory!

Adapted from Various Palliative Care Models, JAMA, ‘01
Optimizing Treatment Requires Individualizing Goals of Care Across the Continuum of Life

- Tumor-directed
- Symptom-directed (palliative)
- Pre-Bereavement
- End of Life

100% ALWAYS

CARE

LIFE CONTINUUM
Individualized Treatment
Over a Life Continuum

Analogous to Writing a Novel Together

“Chapters in Care”

- Add as many “pages” to each chapter
- Be smart & efficient at changing chapters
- Maintain many good next options

The “Binder” of the novel is one’s KPS and Quality of Life
Evidenced-Based Advances in Symptom-Directed Treatment

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## Karnofsky Performance Status (KPS)

<table>
<thead>
<tr>
<th>Value</th>
<th>Level of Functional Capacity</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>Normal, no complaints, no evidence of disease</td>
</tr>
<tr>
<td>90</td>
<td>Able to carry on normal activity, minor signs or symptoms of disease</td>
</tr>
<tr>
<td>80</td>
<td>Normal activity with effort, some signs or symptoms of disease</td>
</tr>
<tr>
<td>70</td>
<td>Cares for self, unable to carry on normal activity or to do active work</td>
</tr>
<tr>
<td>60</td>
<td>Requires occasional assistance, but is able to care for most needs</td>
</tr>
<tr>
<td>50</td>
<td>Requires considerable assistance and frequent medical care</td>
</tr>
<tr>
<td>40</td>
<td>Disabled, requires special care and assistance</td>
</tr>
<tr>
<td>30</td>
<td>Severely disabled, hospitalization is indicated although death is not imminent</td>
</tr>
<tr>
<td>20</td>
<td>Hospitalization is necessary, very sick, active supportive treatment necessary</td>
</tr>
<tr>
<td>10</td>
<td>Moribund, fatal processes progressing rapidly</td>
</tr>
<tr>
<td>0</td>
<td>Dead</td>
</tr>
</tbody>
</table>

Red lines = typical cut-off for routine & investigational treatment

ECOG Performance Status (PS)

• 0-Fully active, able to carry on all pre-disease performance
• 1-Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature
• 2-Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about > 50%
• 3-Capable of only limited self-care, confined to bed or chair > 50%
• 4-Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
• 5-Dead
• Red line = typical cut-off for routine & investigational treatment

Neurologic Functional Status

• **1.** No neurologic symptoms; fully active at home/work without assistance

• **2.** Minor neurological symptoms, fully active at home/work without assistance

• **3.** Moderate neurological symptoms, less than fully active at home/work and requires assistance

• **4.** Severe neurological symptoms, totally inactive requiring complete assistance at home or in institution, unable to work.

www.rtog.org ; others
RPA - Glioma

• **III**: Glioblastoma, KPS 0, age <50
• **IV**: Glioblastoma, KPS 1-2, age <50
• **V**: Glioblastoma, age >50, biopsy-only

Mirimanoff, JCO, 2006; Scott CB, IJROBP, 1998; Curren W, JNCI, 1993
Proposed: Charlson Comorbidity Index

- Ening et al, Retrospective review of 233 new adult Glioblastoma patients at a single tertiary institution in Germany from 2006-2011.

**METHODS:**
- Age, gender, signs, symptoms, KPS, tumor characteristics (size, location, IDH-mutation status, and MGMT-pomoter methylation status), treatment parameters (volumetric EOR and adjuvant therapy).
- Comorbidity status quantified by the Charlson comorbidity index
- Survival analysis by the Kaplan-Maier method. Influence of variables by log-rank test.

**RESULTS:**
- Patients of age > 65 years, KPS ≤ 70, and CCI > 3 were significantly associated with both poor OS (all p < 0.0001).
- Patients of age > 65 years significantly had a CCI > 3 (p < 0.0001).

**CONCLUSIONS:**
- Confirms established prognostic parameters (age and KPS) for Glioblastoma outcome.
- The CCI significantly impacted outcome and may assist pre-operative stratification.

Ening G et al, J Cancer Res Clin Oncol. 2015
KPS is King

- Independent prognostic factor
  - At diagnosis
    - Overall survival
  - At pre-1\textsuperscript{st} resection, adjuvant therapy, pre-2\textsuperscript{nd} resection
    - Overall survival
    - Quality of life

- Essential to receive treatment
  - Clinical trials
  - Routine therapy

- Essential in a Neurosurgeon's discernment on the survival/functional benefits to subsequent resections
  - EOR may be correlated to IDH-1/2-mutation and other molecular-genetic aberrations

- Score is reported differently by provider, caregiver, patient

### KPS in Recent Literature

#### Diagnosis

<table>
<thead>
<tr>
<th>Authors</th>
<th>Nuances</th>
</tr>
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<tbody>
<tr>
<td>Stark AM, Clin Neurol Neurosurg. 2012</td>
<td>also affective d/o effects OS</td>
</tr>
<tr>
<td>Ening G et al, J Cancer Res Clin Oncol. 2015</td>
<td>Charlson comorbidity index</td>
</tr>
<tr>
<td>Chaichana KL et al, World Neurosurg. 2014</td>
<td>achieving a decreased RV and/or an increased EOR is independently associated with survival and recurrence in those patients with tumors with similar resection capacities.</td>
</tr>
<tr>
<td>Beiko J et al, Neuro Oncol. 2014</td>
<td></td>
</tr>
<tr>
<td>Tanaka S et al, J Neurosurg. 2013</td>
<td>idh status improves survival in aggressive resections/CE and nonCE. IDH1 mutant malignant astrocytomas are more amenable to surgical resection and have a survival benefit associated with maximal surgical resection.</td>
</tr>
<tr>
<td>Sanai N et al, J Neurosurg. 2011</td>
<td>elderly age alone not prevent decisions of sx vs biopsy b/c also benefit</td>
</tr>
<tr>
<td>Kumar N et al, J Neurosci Rural Pract. 2013</td>
<td>associated with certain molec./genetic aberrations</td>
</tr>
<tr>
<td>Chaichana KL et al, J Clin Neurosci. 2013</td>
<td>pre-op poor kps - aggressive resection improved post-op kps/os, outcomes and factors associated with survival for poor functioning patients who underwent aggressive resection of their GB</td>
</tr>
<tr>
<td>Chaichana KL et al, J Neurosurg. 2011</td>
<td></td>
</tr>
<tr>
<td>Sacko A et al, J Neurooncol. 2015</td>
<td>KPS &gt; 70 for &gt;73% survival</td>
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#### Pre-1st resection

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<td>Sun MZ et al, J Neurosurg. 2015</td>
<td>KPS &gt; 70 for &gt;73% survival</td>
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<tr>
<td>Han SJ et al, Neurosurgery. 2015</td>
<td>A short delay in the start of concurrent chemoradiation is beyond the classic paradigm of 4 weeks post-resection and may be associated with prolonged OS and PFS.</td>
</tr>
<tr>
<td>Michaelsen SR et al, BMC Cancer. 2013</td>
<td></td>
</tr>
<tr>
<td>Barbagallo GM et al, Neurosurg Focus. 2014</td>
<td>kps not lowered with longterm tmz</td>
</tr>
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#### Adjuvant Tx (ability)

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<tr>
<td>Oppenlander ME et al, J Neurosurg. 2014</td>
<td>as long as kps maintained/no worse neuro fxn, then &gt;80% eor improved survival/outcome. An extent of resection threshold for recurrent glioblastoma and its risk for neurological morbidity. For recurrent glioblastomas, an improvement in overall survival can be attained beyond an 80% EOR. This survival benefit must be balanced against the risk of neurological morbidity, which does increase with more aggressive cytoreduction, but only in the early postoperative period. Interestingly, this putative EOR threshold closely approximates that reported for newly diagnosed Tx at recurrence</td>
</tr>
<tr>
<td>Bloch O et al, J Neurosurg. 2012</td>
<td>aggressive resection at 1st rec improves os/kps if gtr achieved, regardless if initial sx was STR</td>
</tr>
<tr>
<td>Carpentier AF et al, Eur J Neurol. 2012</td>
<td>Steroid-sparing effects of angiotensin-II inhibitors in glioblastoma patients. Lower dex = improved kps/os. Avastin improved qol avastin as valuable palliation with preservation of KPS and an option for steroid withdrawal in patients treated with BEV, supporting the role of this therapy in late-stage disease.</td>
</tr>
<tr>
<td>Adjuvant Tx (ability)</td>
<td>Chaichana KL et al, J Neurosurg. 2011</td>
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<td>Sacko A et al, J Neurooncol. 2015</td>
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<td>Pre-2nd resection</td>
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<td>Tx at recurrence</td>
<td>Oppenlander ME et al, J Neurosurg. 2014</td>
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<tr>
<td></td>
<td>Bloch O et al, J Neurosurg. 2012</td>
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<td></td>
<td>Hofer S et al, Acta Oncol. 2011</td>
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Example: Survival by Pre-operative KPS

- N=100 new Glioblastoma patients, focus: < 60 or > 60 KPS
- observational, 1997-’07, JHH
- **Goal:** factors associated with survival for “poor functioning” < 60 KPS patients undergoing aggressive resections
- Factors associated with improved survival were age <65 year (p = 0.005), tumor size >2 cm (p = 0.01), radical tumor resection (p=0.01), and temozolomide (p = 0.001).
- This study identifies a subset of patients with poor functional status who may benefit from aggressive surgical resection.

Chaichana KL et al, J Clin Neurosci. 2013
KPS Evolves over Lifetime

- N=84, prospective, French institution
- Median survival with KPS ≥ 70 was 14.5 months.
- Patients spent an avg. of 73% of their lifespan with a KPS ≥ 70.
- Surgical resection and low steroid dosage were statistically associated with increased survival time with KPS ≥ 70 (p = 0.015 and p = 0.03, respectively)
- Median survival with KPS ≥ 70 largely exceeds PFS.
Evidenced-Based Advances in Symptom-Directed Treatment

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Specific Symptom Examples

### CNS Anatomy & Function
- Cerebral Edema
- Thrombosis, Hemorrhage
- Obstruction, NPH
- Seizures
- Cognition, Mood, Coping
- Neurologic Deficits, Pain
- Immunosuppression

### Iatrogenic & Co-morbid
- Immunosuppression
- Infection, myelosuppression
- Insomnia
- Endocrine, metabolic
- Fatigue, myopathy
- Drug toxicity
- Fertility, family planning, intimacy, libido
- **Unrelated co-morbidities**

**KEY:** Pursue reversible causes and aggressively treat

---

"Ask your doctor if taking a pill to solve all your problems is right for you"

ASCO POST, 6/2011

Hughes, MA 05; Chang, S JAMA 05; Risk Stratification: Armstrong, Neuro-Onc, 2010
Specific Symptom Examples

CNS Anatomy & Function
- Cerebral Edema
- Thrombosis, Hemorrhage
- Mobility, Deconditioning
- Seizures
- Cognition, Mood, Coping
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Hughes, MA 05; Chang, S JAMA 05; Risk Stratification: Armstrong, Neuro-Onc, 2010; Benson, NEJM, ’70; Dunbar, EM, Cibula, ANO, ’11
Symptom-Directed Treatment

- Immuno-compromise
- Hyper-coagulability
- Marrow dysfunction
- VTE, Hemorrhage
- Hyperglycemia, Immunosuppression, Infection
- Edema, Inflammation
- Avastin, Steroids
- Mobility, Deconditioning, Deficits
Symptoms & KPS Evolution Requires Ongoing Treatment

Radio-graphic & Often Clinical “worsening” for ~ 2-6+ mo. before improvement

Symptoms Accumulate
Steroids

- **No consensus in management** [Deutch MB et al, J Neurooncol. 2013; Chang SM et al, JAMA, 2005]

- **Decadron is best for CNS**
  - More glucocorticoid, Less mineralocorticoid [various]
  - BID frequency is sufficient
  - Plethora of short and long-term SEs
  - **Cumulative dose correlated to lower KPS and OS** [Michaelsen SR et al, BMC Cancer. 2013]

- **Hyperglycemia correlated to:**

- **Strategies to minimize hyperglycemia include:**
  - *(Modified)* Ketogenic diet [Champ CE et al, J Neurooncol. 2014; Blakeley et al, JNO, in-press]
  - Non-steroid “alternatives” are not adequate – e.g., mannitol, diamox, loop diuretics, VEGF agents, trial agents [Wen, P, et al, Neuro 08; Aenlle, L, Kesari, S, Dunbar, EM, ANO, ‘11, Dunbar; various]
Immunosuppression
Example: Lymphopenia from Glioma, Steroids, RT, etc..

Consider CD4 count; Bactrim, Dapsone, Pentamidine

Dunbar, E, Grossman, SA, NOIU, used by permission, 06
Lymphopenia-related Infections

- Fungal, atypicals, parasites, less likely bacteria
- Viruses, e.g., CMV, Zoster, Hepatitis, Pertussis/Diphtheria
- **U.S. Standard Practice:** PJP prophylaxis in Malignant Gliomas undergoing RT (regardless of steroids, chemo):
  - Bactrim improves OS and lowers infections, including hospitalizations [Hughes MA et al, IJROBP, 2005; various]
- Non-infectious hepatitis correlated to temozolomide +/- concurrent AEDs (valproic acid) [Grieco A et al, Medicine (Baltimore). 2015; Neyns B et al, Acta Neurol Belg. 2008]
VEGF Agents

- The VEGF pathway is key to both angiogenesis and vascular permeability
- Alters the Blood Brain Barrier
  - T1-CE MRI, Vasogenic Edema & Mass-effect
- Tumor-directed roles:
  - 2009 U.S. FDA approved Monoclonal Ab against the extracellular VEGF-R in for progressed Glioblastoma, based on RR & PFS. Wide extrapolation
  - Clinical trials are focusing on overcoming resistance patterns and maximizing mechanisms

Vredenburg JJ, CCR 07 and JCO 07
VEGF Agents

- **Symptom-directed (Palliative) roles:**
  - Radiation-necrosis, vasculopathy
  - Angioedema
  - Macular degeneration

- **Expensive!**

- **Altered patterns of imaging, progression and resistance**

  * **RANO criteria** [Chang, et al, N-O, 07; various]

Vredenburg JJ, CCR 07 and JCO 07
VEGF Agents

- Unique safety & monitoring
  - Not a “chemo”
  - ~21-28 D½ life of “vascular sequela”, including de novo arterial/venous hemorrhage, thrombosis; acceleration of CVA, CAD, HTN, vascular renal dz; wound dehiscence, & poor wound healing, fatigue, PML, etc..
  - No “antidote”
  - Peri-Surgical Safety:
    - Hold ~28 days for major elective surgery (a minimum of 4-6 wks if 2nd Glioma resection)
    - Hold ~14 days for minor surgery [various]
  - ? Effect on fertility

Vredenburg JJ, CCR 07 and JCO 07; http://imagebank.hematology.org/Content%5C672%5C3671/3671_t.JPG
VTE & Hemorrhage

- STUPP protocol: 20% mild thrombocytopenia and 5% have severe [Stupp R et al, 2005]
- VTE & hemorrhage occur in ≤ 35% of Malignant Gliomas [Chang SM, JAMA, 2005; various]
- To-date industry trials evaluating prophylactic LMWH in new Glioblastoma have been stopped 2/2 increased hemorrhage and/or lack of efficacy
- Modern algorithms for VTE and hemorrhage in CNS tumor patients are minimizing toxicity [Strowd RE 3rd, et al, Curr Treat Options Onc. 2012; Gerber DE et al, JCO, 2006]
- Modern use of LMWH may be improving outcomes [Zincircioglu SB et al, J BUON. 2012]
- Newer mechanisms of AC may be more safe and efficacious, e.g., Direct-thrombin-inhibitors [www.uptodate.com; Expert Review of Neurotherapeutics, Morales-Vidal S et al, 2012]
  - After 4-6 from last resection
  - On AC for VTE (after acute) or after SDH/SAH (after acute)
  - -On anti-PLT therapy
- Alternatives or adjuncts include: compression stockings, intermittent compression devices, and minimizing steroids, inflammation, trauma [various]
Other Symptoms with Increasing Evidence-Based Treatment

Cognition, Memory, Mood, Motility (2nd Parkinsonism), Sleep Disorders, Fatigue, Hypersomnia:

- Reversible acetylcholinesterase inhibitors
  - Donepezil
- NMDA receptor blockers
  - memantine
- Central (psycho)-stimulants
  - Methylphenidate & Modafinil
- Dopamine-Agents
  - Methylphenidate
  - Levo-Dopa & Similar
- Serotonin-Norepinephrine Re-Uptake Inhibitors
- Sleep continuity agents
- Neuropathic pain agents
  - Gabapentin, pregabalin

Nausea, Endocrine, Bone Health, Fall-prevention, Cataracts, etc.

Shaw E, JCO, 3/06; Wen P, JCO 06; Gehring K, J NeuroOncol, 10/11; Butler JM, JROJP, 12/07; Kumar R, Drugs 08; Bruera E, JCO, 5/06; Mar Fan HG, Support Ca Care, 6/08; Roony JNCI 1/11; Vargo M, AMJMR, 5/11; Parcel, Cancer 1/10; Brown, PD, et al, Neuro Oncol., Oct. 2013; Minton, O et al, Jr of Pain and Symptom Mgmt, 2011; Gehring, K et al, J Neurooncol., Mar 2012; Campos, MPO, et al, Annals of oncology, 2011
Summary of Treatments that Impact Symptoms & KPS Through Time

- Hepatitis +/− viral titers
- Vaccines
- CBC/diff q wk
- PJP prophylaxis
- +/- CMP (Glucose, TAs)
- +/- AED levels
- Least-needed Decadron
- Mobility, Conditioning
- H&Ps by experienced providers (VTE, hemorrhage, infections, etc.)
- CBC/diff q ~ mo.
- +/- PJP prophylaxis
- H&Ps by experienced providers (progression vs. pseudo-progression, delayed sequel of treatments)
- Endocrine, bone density, cataracts, emotional, etc.
- Eye, rtn to wk/drive evals.
- Fertility, libido, etc.
Evidenced-Based
Symptom-Directed Treatments

Questions?

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