Seizures in Neuro-Oncology

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Disclosure of Conflicts of Interest

Charles Vecht MD PhD has received consultancy fees from UCB Pharma; Research grants from UCB Pharma, Eisai, and GlaxoSmithKline; and funding for travel from UCB Pharma.
Management of Brain Tumor-Related Epilepsy (BTE)

• Seizures as Presenting and Prognostic Sign
• Shared Mechanisms of Seizure and Glioma
• Evidence-Based Choices of AEDs
• Interaction of AEDs with Survival: Valproic Acid
# Seizure Characteristics in Gliomas

<table>
<thead>
<tr>
<th></th>
<th>Glioneuronal Tumors</th>
<th>Low-grade Glioma</th>
<th>Glioblastoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at Presentation</td>
<td>15 - 21 yr</td>
<td>38 - 40 yr</td>
<td>60 yr</td>
</tr>
<tr>
<td>Seizures at Presentation</td>
<td>60 - 100 %</td>
<td>65 - 85 %</td>
<td>42 %</td>
</tr>
<tr>
<td>Overall Seizure Frequency</td>
<td>80 - 90 %</td>
<td>70 - 90 %</td>
<td>60 %</td>
</tr>
<tr>
<td>Refractory Sz. after Surgery</td>
<td>10 - 30 %</td>
<td>30 - 35 %</td>
<td>15 %</td>
</tr>
</tbody>
</table>

Englot, 2011; 2012; Kerkhof 2013
Independent Prognostic Factors for Survival in LGG

Seizures as Presenting Sign
Age < 50 years
Extensive Tumor Resection

Van Veelen 1999; Pignatti 2002; Jakola 2012; Pallud 2014
## Independent Prognostic Factors in GBM

<table>
<thead>
<tr>
<th>Factor</th>
<th>Hazard Ratio : Prolonged Functional Independence</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preop. KPS score ≥90</td>
<td>0.72 (0.58–0.89)</td>
<td>0.004</td>
</tr>
<tr>
<td>Preop. Seizures</td>
<td>0.60 (0.43–0.83)</td>
<td>0.002</td>
</tr>
<tr>
<td>GTR</td>
<td>0.57 (0.46–0.71)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>TMZ / RT</td>
<td>0.62 (0.48–0.78)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Chaichana 2009
## Survival Outcome in Glioblastoma (n = 291)

| Treatment                           | Survival Rate  
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Recieving Chemoradiation with Temozolomide (Study period 1/1999 - 4/2012)</td>
<td>56.7% (165)</td>
</tr>
<tr>
<td>Survival (without epilepsy)</td>
<td>8 months</td>
</tr>
<tr>
<td>Survival (with epilepsy)</td>
<td>14 months</td>
</tr>
</tbody>
</table>

Kerkhoff 2013
### Recurrent Seizures May Indicate Tumor Progression

<table>
<thead>
<tr>
<th></th>
<th>% of Recurrent Sz. as Sign of Tumor Progression</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-Grade Glioma</td>
<td>41 /79 pts (52%)</td>
<td>HR 3.8 (CI 1.7-8.3) p.03</td>
</tr>
<tr>
<td>High-Grade Glioma</td>
<td>24 /37 pts (65 %)</td>
<td>HR 2.6 (CI 1.3-6.0) p.006</td>
</tr>
</tbody>
</table>

Chang 2008; Chaichana 2009
Glioma and Seizures: Role of Glutamate

Buckingham 2011; Simon 2011; Liubinas 2014
Talampanel with standard radiation and temozolomide in patients with newly diagnosed glioblastoma: a multicenter phase II trial.

No. at risk
RT + TMZ + Talampanel  60  56  47  34  25
RT + TMZ (EORTC) 1  287  248  174  109  57

Grossman 2009
Regulation of PI3K / PTEN / Akt / mTOR Signalling

Lim, 2015
Everolimus Treatment of Refractory Epilepsy in Tuberous Sclerosis Complex

Franz 2013; Krueger 2013
Seizure-Free Outcome after Surgery in Low-grade Gliomas (572 pts in 14 series)

<table>
<thead>
<tr>
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<th>Engel I</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Operatively</td>
<td>23,9 %</td>
</tr>
<tr>
<td>Seizure-free</td>
<td>«Medically Controlled»</td>
</tr>
<tr>
<td>Post-Operatively</td>
<td>69,2 %</td>
</tr>
<tr>
<td>Seizure-free</td>
<td></td>
</tr>
</tbody>
</table>

Smits 2011; You 2012
Effect of Radiation Therapy and of Systemic Chemotherapy

Seizure-Freedom after RT:
  EORTC in LGG (n = 314) 75 % vs. 59 % (p<.03)
  Ruda (n = 43) 76 %

Temozolomide in Low-grade Gliomas
  TMZ Cohort n =39; Control group n= 30
  > 50 % Decrease in Sz frequency:
    With TMZ 59 % vs. 13 % (p < .001)

Van den Bent 2005; Sherman, 2011; Ruda 2013
Which AEDs to use in the Clinical Practice of Neuro-oncology?
Choice of AEDs for Brain Tumours

- Partial-onset Seizures in Adults
  (Localization-Dependent, Focal, Symptomatic)

- Individual Patient factors:
  Age
  Sex
  Organ Dysfunction (Liver, Kidney)
  Co-Morbidity
  Co-Therapy

Shorvon 2012
• Adults with Partial-Onset Epilepsy
  (Class I: 4; Class II: 1; Class III: 34 Studies)

• Level A: CBZ, LEV, PHT, ZNS

• Level B: VPA

• Level C: GBP, LTG, OXC, PB, TPM, VGB
Potential Drug Interactions between Anti-Epileptic Drugs (AEDs) and Chemotherapeutic Drugs (CTDs)

To Avoid Enzyme-Inducing AEDs:
- Carbamazepine
- Phenytoin
- Phenobarbital

All Enzyme-Inducers of 2B6, 2C9, 2C19 and 3A4

AAN Glantz 2000; EANO Soffietti 2010
Evidence-based Choice of AEDs in Tumor-Related Epilepsy

- **Level A:** LEV, ZNS
- **Level B:** VPA
- **Level C:** GBP, LTG, OXC, TPM, VGB

AAN Glantz 2000; Brodie 2013; Glauser 2013
Levetiracetam Monotherapy in Brain Tumors

• > 50 % Seizure Response: 92 - 95 %

• Seizure-Free Rate: 63 - 93 %

Wagner, 2003; Partap 2008; Maschio 2010; Lim 2009; Usery 2010
Comparison of Response and Withdrawal Rates in Meta-analyses of Add-on AEDs vs. Placebo

Otoul 2005
LEV improves Encoding, Storage, and Active Retrieval of Words remembered
Evidence-based Choice of AEDs in Brain Tumor-Related Epilepsy

- Level A: LEV, ZNS
- Level B: VPA
- Level C: GBP, LTG, OXC, TPM, VGB

AAN Glantz 2000; Brodie 2013; Glauser 2013
Efficacy and Tolerability of AEDs for Refractory Focal Epilepsy

Meta-Analysis

Bodalia, 2013
# Effect of valproic acid on seizure control and on survival in patients with glioblastoma multiforme

<table>
<thead>
<tr>
<th>Initial Therapy</th>
<th>Seizure-Freedom</th>
</tr>
</thead>
<tbody>
<tr>
<td>VPA Monotherapy</td>
<td>28 / 36 (77.8 %)</td>
</tr>
<tr>
<td>LEV Monotherapy</td>
<td>25 / 36 (69.5 %)</td>
</tr>
<tr>
<td>VPA &amp; LEV Polytherapy</td>
<td>38 / 63 (60.3 %)</td>
</tr>
</tbody>
</table>

Kerkhof, 2013
Survival w/o Enzyme-Inducing in GBM and Adjuvant CCNU

<table>
<thead>
<tr>
<th></th>
<th>A (# 88) No Seizures</th>
<th>B (# 43) Seizures</th>
<th>C (# 37) Seizures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjuvant CCNU</td>
<td>EI-AEDs</td>
<td>Non EI-AEDs</td>
<td></td>
</tr>
<tr>
<td>(Lomustine)</td>
<td>CBZ (81 %)</td>
<td>VPA (85 %)</td>
<td></td>
</tr>
<tr>
<td>Survival</td>
<td>11.6</td>
<td>10.8</td>
<td>13.9*</td>
</tr>
<tr>
<td>(in months)</td>
<td></td>
<td></td>
<td>p 0.016</td>
</tr>
</tbody>
</table>

Oberndorfer, 2005
Prolonged survival with valproic acid use in the EORTC/NCIC temozolomide trial for glioblastoma

M. Weller, MD, T. Gortlia, MSc, PhD, J.G. Cairncross, MD, M.J. van den Bent, MD, W. Mason, MD, K. Belanger, MD, A.A. Brandes, MD, U. Bogdahn, MD, D.R. Macdonald, MD, P. Forsyth, MD, A.O. Rossetti, MD, D. Lacombe, MD, R.-O. Mirimanoff, MD, C.J. Vecht, MD and R. Stupp, MD

HR & CI*  

<table>
<thead>
<tr>
<th>AED status</th>
<th>TMZ/RT (RT)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No AED</td>
<td>0.64</td>
<td>(0.46 ; 0.89)</td>
</tr>
<tr>
<td>VPA only</td>
<td>0.41</td>
<td>(0.26 ; 0.65)</td>
</tr>
<tr>
<td>EIAED only</td>
<td>0.69</td>
<td>(0.53 ; 0.89)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>0.62</td>
</tr>
</tbody>
</table>

n = 277  EIAED  
135  non-EIAED  
97  VPA

Weller, 2011;  Kerkhof 2013
Valproic Acid With Temozolomide/Radiation in High-Grade Gliomas
NCT00302159

n = 43

Median Survival: 29 months

Med. Progression Free-Survival: 10.5 months (C.I. 7-51)

Camphausen, 2015
Valproic Acid

Free Fatty Acid
Histone Deacetylase Inhibitor (HDACi)
Haemato-Toxicity of Valproic acid, Levetiracetam and Controls with TMZ/RT in GBM
Impact of antiepileptic drugs on thrombocytopenia in glioblastoma patients treated with standard chemoradiotherapy

Maria Simó, Roser Velasco, Francesco Graus, Eugenia Verger, Miguel Gil, Estela Pineda, Jaume Blasco, Jordi Bruin

<table>
<thead>
<tr>
<th>Variables</th>
<th>Coefficient</th>
<th>SE</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelets analyzed as a continuous variable⁴</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex (men)</td>
<td>9.2251</td>
<td>6.4844</td>
<td>0.16</td>
</tr>
<tr>
<td>Age</td>
<td>-1.3282</td>
<td>0.2812</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TMZ</td>
<td>-0.0113</td>
<td>0.0014</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>VPA</td>
<td>-20.0045</td>
<td>6.9851</td>
<td>0.004</td>
</tr>
<tr>
<td>LEV</td>
<td>0.6802</td>
<td>8.7939</td>
<td>0.938</td>
</tr>
<tr>
<td>Constant</td>
<td>323.3569</td>
<td>17.4665</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Platelets analyzed as a dichotomic variable (&lt;100.000/m)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex (men)</td>
<td>-0.215</td>
<td>0.1796</td>
<td>0.23</td>
</tr>
<tr>
<td>Age</td>
<td>0.0013</td>
<td>0.0079</td>
<td>0.87</td>
</tr>
<tr>
<td>TMZ</td>
<td>0.0001</td>
<td>0.00004</td>
<td>0.001</td>
</tr>
<tr>
<td>VPA</td>
<td>0.2914</td>
<td>0.1874</td>
<td>0.12</td>
</tr>
<tr>
<td>LEV</td>
<td>-0.1498</td>
<td>0.2614</td>
<td>0.57</td>
</tr>
<tr>
<td>Constant</td>
<td>-2.1305</td>
<td>0.493</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Conclusions

Evidence-Based Choices in BTE

• Levetiracetam (level 1) and Valproic Acid (level 2)
• Well-tolerated
• No Harmful Metabolic Drug Interactions

• Adverse Effects:
  – LEV: Irritability, Aggression in 5-7%
  – VPA: Hematological Toxicity

• LEV and VPA: Synergistic Anti-Epileptic Activity?
• TMZ and VPA: Synergistic Anti-Tumor Activity?
Towards a Unisono Therapy for BTE?

- Anti-Tumor Therapy: Surgery, Radiation & Chemotherapy

- Role of Glutamate & AMPA-blockers

- mTOR-inhibitors

- Role of Valproic Acid as HDAC inhibitor

Buckingham 2011, Weller 2011, Kerkhof 2013, Ruda 2013
Closing the Gap between Separate Anti-Epileptic and Anti-Tumor Therapy ?
Site on Drug Interactions

- [http://medicine.iupui.edu/clinpharm/ddis/](http://medicine.iupui.edu/clinpharm/ddis/)

If LEV/VPA are Insufficient, to Choose between

- **Lacosamide**,  
  As Add-on, No Interactions

- **Lamotrigine**  
  Well tolerated, Synergism with Valproate

- **Zonisamide**  
  Level 1 Monotherapy, Few Interactions

Sogawa 2009; Van Breemen 2009; Maschio 2011; Saria 2013; Baulac 2013
Recommendations in Brain Tumors

• Consensus Guidelines to Avoid Enzyme-Inducing AEDs
  i.e. Phenytoin, Carbamazepine, Phenobarbital

• In newly diagnosed Brain Tumors, No Prophylaxis with AEDs

• In newly diagnosed Brain Tumors without Sz, Taper/Discontinue AEDs after 1st Post-operative Week/Month

AAN: Glantz 2000; Soffietti 2010
Maschio, 2009

**Efficacy and tolerability of zonisamide as add-on in brain tumor-related epilepsy: preliminary report**

M. Maschio\(^1\), L. Dinapoli\(^1\), F. Saveriano\(^2\), A. Pompli\(^3\), C. M. Carapella\(^3\), A. Vidiri\(^4\), B. Jandolo\(^1\)

\( n = 6 \)

Mean seizures number prior to ZNS: \( 27.7 / \) month.

At last Follow-up: Mean seizure number: \( 8.8 / \) month

Responder Rate: 83.3%

ZNS mean dosage: 280 mg/day

Two patients disc’d ZNS because of Side-effects

No other reported Side-effects
Kaplan-Meier Curve of GBM Patients \((n = 291)\) with Chemoradiation by TMZ with and without VPA

- VPA & TMZ > 3 Mos \((n=108)\)
- No VPA or <3 Mos \((n = 57)\)

**Median Progression Free Survival**
- 10.5 (CI 7-51) \(n = 43\)

**Progression Free Survival**
- 6 months 70 %
- 12 months 43 %
- 24 months 38 %

**Med. Survival**
- 69 wks [CI:61.7-67]
- vs. 61 wks [CI:52-69]

\(P= 0.016\)

\(HR 0.63 [95\% 0.43-0.92]\)

Kerkhof, 2013
Dosages to Use

- Levetiracetam  1000 - 3000 mg
- Valproic Acid  1000 - 3000 mg (20 mg/kg)

- Second Line: Add-on / Polytherapy (in Combination)
  - Levetiracetam  1000 - 2000 mg
  - Valproic Acid  1000 - 1500 mg

Wagner 2003, Van Breemen 2009, Kerkhof 2013
Etiological Factors and AED Resistance

Gilioli 2012
Mechanistic Target of Rapamycin (mTOR) in Tuberous Sclerosis Complex-Associated Epilepsy

Curatolo, 2015
Prophylaxis with LEV vs. PHT in 1\textsuperscript{st} Post-Operative Week

<table>
<thead>
<tr>
<th></th>
<th>LEV</th>
<th>vs.</th>
<th>PHT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizures in 1\textsuperscript{st} week</td>
<td>1/105</td>
<td></td>
<td>9/210 (NS)</td>
</tr>
<tr>
<td>Adverse Drug Reactions</td>
<td>1/105</td>
<td></td>
<td>38/210</td>
</tr>
<tr>
<td>Sz. after 1 yr Follow-up</td>
<td>26 %</td>
<td></td>
<td>36 %</td>
</tr>
<tr>
<td>Retent. Rate after 1 yr</td>
<td>64 %</td>
<td></td>
<td>26 %</td>
</tr>
</tbody>
</table>

«Data suggest that it is safe to switch from PHT to LEV monotherapy«

Milligan, 2008; Lim 2009