What’s New in Neuro-Oncology: Updates from Recent ASCO Meetings

Sponsored by the University of Chicago Brain Tumor Center & the Heinrich Kluver Memorial Lectureship Endowment
Welcome and Introduction

Infiltrating gliomas remain the most common and, therefore, vexing, clinical problem in neuro-oncology. Significant advances in patient outcomes have been slow, despite substantial investments of creative thinking, time, energy, and financial resources.

Our goals are: 1) to review recent clinical trial results and 2) to discuss their impact on future directions and challenges in providing optimal care.
PROBLEMS UNIQUE TO NEURO-ONCOLOGY

• Small changes in tumor size and location can have significant impact on functional status.

• Brain anatomy and physiology limit therapeutic options.
  – Surgery
  – Radiotherapy
  – chemotherapy
PROGRAM

• Bevacizumab in Glioblastoma
  • M. Kelly Nicholas, MD, PhD

• Anaplastic Gliomas
  • Rimas Lukas, MD

• Combining Chemotherapy and Radiotherapy in Low Grade Gliomas
  • Steve Chmura, MD, PhD

DISCUSSION
ANAPLASTIC GLIOMAS: The Impact of Recent Developments on Treatment Approaches
OVERVIEW

• Epidemiology
• IDH1
  – Recently described prognostic marker
• Anaplastic Astrocytomas (AA)
  – Role of RT and TMZ
• Anaplastic Oligodendroglialomas (AO)
  – Role of RT and chemo
Figure 5.
Distribution of All Primary Brain and CNS Tumors by Histology
(N=158,088)

CBTRUS Statistical Report: NPCR and SEER Data from 2004-2006

Glioblastoma 17.1%
Astrocytomas 6.8%
Ependymomas 1.9%
Oligodendrogliomas 2.1%
Embryonal, including Medulloblastoma 1.0%
Meningioma 33.8%
All Other 12.7%
Lymphoma 2.4%
Nerve Sheath 8.7%
Craniopharyngioma 0.7%
Pituitary 12.7%

Gliomas (ICD-O-3: 9380-9384, 9391-9460, 9480) account for 32% of all tumors and 80% of malignant tumors
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GLIAL TUMORS

GLIOMAS

ASTROCYTOMAS

OLIGODENDROGLIOMAS

EPENDYMAL TUMORS

Grade I
Grade II
Grade III
Grade IV

Grade I
Grade II
Grade III
Grade IV

The University of Chicago Medicine & Biological Sciences
GLIAL TUMORS

ASTROCYTOMAS

OLIGODENDROGLIOMAS

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Grade I
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Grade I
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IDH Mutation

- Somatic mutations
- ↓ability to convert isocitrate [ICT] → áketoglutarate [áKG]
- now áKG → R(-)-2-hydroxyglutarate [R(-)-2HG]
  - Consumes NADPH
    - → ?sensitization to RT & chemo?
- ↑HIF-1-á

IDH Mutation

• **IDH1**
  – NADP+ dependant
  – Protein in cytoplasm, peroxisomes, ER.
  – Codon 132
  – IHC for mIDH1R132H for mutation
  – No mutations in non-glial brain tumors, but present in other cancers (ALL, AML, prostate)
  – In astro and oligo

• **IDH2**
  – NADP+ dependant
  – Protein in mitochondria
  – Codon 172
  – Only in glial tumors without IDH1 mutations
  – In oligo

• **IDH3, 4, 5**
  – NAD+ dependant
  – Protein in mitochondria
  – No known mutations in glioma

IDH Mutation

- Oligodendrogliomas (50-80%)
- Oligoastrocytomas (~95%)
- Astrocytomas (20-90%)
- sGBM (70-85%) vs pGBM (2-5%)

IDH Mutation

- Never occur after 1p19q LOH or p53 mutation
- → very early event in gliomagenesis
- Correlation between IDH1 mutation and MGMT promoter hypermethylation
- Inverse correlation w/ EGFR amplification
- Correlation w/ young age

AA

- Open-label, phase II
- N=162, AA+AOA
- @1\textsuperscript{st} relapse
- TMZ 200 mg/m\textsuperscript{2} 5/28d
- PFS\textsubscript{6}=46%
- PFS=5.4mo, PFS\textsubscript{12}=24%, OS=13.6mo
- RR=35% (CR=8% + PR=27%)
- HQL improved in pts w/ PFS at 6 mo

(Yung, et al. JCO. 1999)
AA

NCCN Guidelines

• AA  → RT (Category 1)
  → RT+TMZ (Category 2A)
  → TMZ or PCV (Category 2A)

• AA (or AOA or OA) w/ KPS<70
  → RT (hypofrac or standard) (Category 2A)
  → TMZ or PCV (Category 2B)
  → Palliative/Best Supportive Care (Category 2A)
1p/19q FISH

Ratio 1p/1q = 0.54

Ratio 19q/19p = 0.55
EORTC 26951

- Phase III, n=368, median f/u=140 mo
- AO
- RT 59.4 Gy→PCV X 6  vs. RT alone
- OS 42.3mo vs. 30.6mo, HR 0.75, 95%CI, .6-.95
- 1p19q deleted OS not-reached vs. 112mo, HR 0.56, 95%CI, 0.31-1.03
- IDH1 mutation (retrospective eval in 179 pts)
  - OS 8.4yr vs. 1.4yr
EORTC 26951

Randomly assigned (N = 368)

Allocated to RT/PCV (n = 185)
- Never started RT (n = 5)
- Early PD (n = 1)
- Patient refusal (n = 2)
- Other (n = 2)
- Never started PCV (n = 19)

Allocated to RT (n = 183)
- Randomly assigned in wrong trial (n = 1)

Progression (n = 137)
- Further treatment (n = 72)
  - Any chemotherapy (n = 120)
  - PCV (n = 90)
  - Temozolomide (n = 65)

Progression (n = 161)
- Further treatment (n = 13)
  - Any chemotherapy (n = 13)
  - PCV (n = 90)
  - Temozolomide (n = 65)

(van den Bent M J et al. JCO 2013;31:344-350)
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Progression (n = 137)
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  - Any chemotherapy (n = 72)
    - PCV (n = 13)
    - Temozolomide (n = 55)
  - Other (n = 65)

Progression (n = 161)
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(van den Bent M J et al. JCO 2013;31:344-350)
Progression-free survival in both treatment arms for (A) patients with 1p/19q-codeleted tumors (n = 80) and (B) patients with non–1p/19q-codeleted tumors (n = 236).

(van den Bent M J et al. JCO 2013;31:344-350)
Overall survival in both treatment arms for (A) the patients with 1p/19q-codeleted tumors (n= 80) and (B) the patients with non–1p/19q-codeleted tumors (n = 236).

(van den Bent M J et al. JCO 2013;31:344-350)
RTOG 9402

• Phase III, n=291, median f/u=5yr
• AO or AOA
• PCV X 4→RT 50.4 Gy vs. RT 50.4 Gy
• CCNU (130 mg/m$^2$)D1, procarbazine (75 mg/m$^2$)D8-21, Vincristine (1.4 mg/m$^2$)D8,29
• OS 4.6yr vs. 4.7yr (p=0.1)
• 1p19q deleted OS 14.7yr vs. 7.3yr, HR 0.59, 95%CI 0.37-0.95 (p=0.03)
RTOG 9402

(Cairncross, et al. JCO. 2013)
RTOG 9402

(Cairncross, et al. JCO. 2013)
RTOG 9402

(Cairncross, et al. JCO. 2013)
1p19q non-codeleted patients.

HR=0.85

95% CI 0.58-1.23,
P=0.39
PCV vs. TMZ

• Retrospective
• N=1001
• OS 7.6yr vs. 3.3yr

(Lassman, et al. Neuro Oncol 2011)
(Lassman, et al. Neuro Oncol 2011)
NOA-04

- Phase III
- Anaplastic gliomas
  - Minority of pts w/ 1p19q codeletion
- RT vs. Chemo (TMZ or PCV)
- Cross-over at progression
- No difference in TTP
- TMZ more tolerable
CATNON

- NCT00626990
- Primary endpoint OS
- Secondary endpoints: PFS, neurological deterioration-free survival, safety, late cognitive effects, QOL

**ARMS**
- RT alone
- RT/TMZ
- RT→TMZ (5/28) X 12
- RT/TMZ→TMZ (5/28) X 12
Codel

**ORIGINAL ARMS**
- RT alone
- RT/TMZ → TMZ
- TMZ

**CURRENT ARMS**
- RT → PCV
- RT/TMZ → TMZ
- TMZ

NCT00887146
Monsueto Library, 57th St & Ellis Avenue