INTERMEDIATE GRADE GLIOMA - THE ROLE OF CHEMOTHERAPY AND RADIOTHERAPY

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Disclosures
None

Outline
- Definition
- Current trends in diagnosis
- Management at initial diagnosis, including clinical trials
- Management at time of relapse

Definition of intermediate grade glioma
- Grade III by WHO histologic classification
- Includes histological subtypes of astrocytoma, oligodendroglioma, mixed oligo-astrocytoma

Note: Anaplastic ependymoma will not discussed in this presentation
Diagnosis

- Following clinical signs and symptoms concerning for an intracranial mass, standard evaluation is for a Magnetic Resonance Imaging scan.
- Although contrast enhancement can be seen in patients with anaplastic glioma, these can also be predominantly non-enhancing.
- Calcification on CT and hemorrhage may be seen in oligos.
- Physiologic techniques using spectroscopy, cerebral blood volume and apparent diffusion coefficient demonstrate heterogeneity of the disease.

Heterogeneity of Gliomas on MRI

Examples of spectra from normal tissue and tumor.
Pathology

- Grade III by WHO histologic classification - Based on cellularity, pleomorphism, mitotic activity, endothelial proliferation and necrosis
- Different criteria for astrocytic versus oligodendroglial origin
- Histologic assessment can be subjective, especially among the mixed tumors, with high inter-observer variability (20-30% variability)
- Despite tumors of similar histology and grade, clinical outcome is variable
- Need for more objective assessment that correlates with clinical outcome

Malignant glioma

- Need for more objective assessment that correlates with clinical outcome
- Chemotherapy responsiveness of anaplastic oligodendroglioma by Cairncross et al in 1988 prompted an evaluation of potential predictive markers
- Landmark study in 1998 by Cairncross demonstrated the link between molecular genetics and clinical outcome - loss of 1p/19q was associated with favorable therapeutic response and longer survival times
Molecular alterations

Oligodendrocytes or precursor cells
- LOH 1p
- LOH 19q
- LOH 4q
- IDH mutation
- EGFR
- PDGF/PDGFR overexpression

Oligodendroglioma WHO grade II
- CDKN2A deletion
- CDKN2C mut/del
- LOH 9p and 10q
- CDK4, EGFR, MYC
- Amplification
- VEGF overexpression

Anaplastic oligodendroglioma WHO grade III

Adapted from Kleihues and Cavenee

Molecular/cytogenetic changes in astrocytic tumors

Differentiated astrocytes or precursor cells
- Grade II astrocytoma
  - LOH 19q (~50%)
  - RB alteration (~25%)
- Anaplastic astrocytoma
  - LOH 10q
  - PTEN mutation (5%)
  - PDGFR amplification (<10%)
- Secondary glioblastoma

Anaplastic oligodendrogloma
- 2 phase III randomized studies performed
- RTOG - XRT vs intensive PCV and XRT
- EORTC - XRT vs XRT followed by PCV
- Preliminary reports in 2006 did not demonstrate a survival advantage however updated results were published in 2013

Van den Bent et al JCO 2013, Cairncross et al JCO 2013

Updated results of 2 randomized trials in AO

Van den Bent et al JCO 2013, Cairncross et al JCO 2013
Results

RTOG 94-02
- 291 patients accrued
- 70% of patients with pure AO
- 68% age < 50 years
- 148 on chemo-XRT, 143 on XRT alone
- Groups were balanced for age, KPS
- Tumor tissue for 1p 19q available for 70%

EORTC 26951
- 368 patients accrued
- 72% of patients with pure AO
- Median age = 49
- 185 on XRT-chemo, 183 on XRT alone
- Groups were balanced for age, KPS
- Tumor tissue for 1p 19q available for 85%

Van den Bent et al JCO 2013, Cairncross et al JCO 2013

Initial Results (2006) PFS

Initial Results (2006) OS

RTOG 94-02

EORTC 26951

Initial results of survival (2006) based on genotype/treatment : RTOG 9402
Maturation of results with molecular information acquired for 86-90% of patients.

Van den Bent et al JCO 2013, Cairncross et al JCO 2013

Clinical implications
- Clear difference in outcome based on 1p19q status demonstrating predictive importance of molecular stratification
- Highlights importance of tissue acquisition and long term follow up
- Radiation alone can no longer be considered the standard of care for 1p19q codeleted AO
- Data supports upfront treatment with radiation/chemotherapy
- What is optimal paradigm?
  - Chemo then XRT or XRT then chemo
  - Role of temozolomide vs PCV
  - Temozolomide alone, or concurrent/adjuvant
  - Ongoing clinical trial addresses these questions

Van den Bent et al JCO 2013, Cairncross et al JCO 2013
Ongoing Phase III Intergroup AG Studies: Treatment Assignment based on molecular markers

Newly Diagnosed AO, AOA or AA by Central Review
Assess 1p/19q

- 1p/19q deletion
  - N0577 Phase III co-deleted AG trial
- No 1p/19q deletion
  - EORTC 26053 Phase III non-co-deleted AG trial

NCCTG N0577: Phase III Anaplastic glioma with 1p/19q LOH

- Newly Diagnosed AO/AA 1p/19q co-deletion
- RT (5960cGy)/PCV
- RT + TMZ → TMZ (Stupp)
- TMZ x 12 cycles

Translational correlates
1p/19q translocation
IDH mutation
MGMT promoter methylation
QOL/neurocognition

Primary endpoint: Time to progression

EORTC 26053: Phase III Anaplastic Glioma without 1p19q LOH

- RT + Temozolomide
  - No Adjuvant Temozolomide
- RT alone
  - Adjuvant Temozolomide

Stratified by MGMT status
Primary End Point: Overall Survival

Adjuvant Chemotherapy prior to RT for anaplastic oligodendroglioma

- RTOG 0131 (Vogelbaum et al; Neuro-Oncol 2009)
- Treatment Plan: Single arm Phase II study of pre-irradiation TMZ (150mg/m²/day on a 7on/7off schedule) for 6 cycles, followed by chemoradiotherapy for grade III oligo and mixed tumors
- Endpoint was response rate during the 6 months of neoadjuvant TMZ
- Objective response rate was 32% (6% CR, 26% PR)
- 10% progressed on TMZ (compared to 20% in RTOG 9402 when intensive PCV was given neoadjuvantly)
Efficacy and safety of initial RT versus PCV or temozolomide chemotherapy in 392 patients with grade III tumors (Wick et al, JCO 2009). Primary endpoint was TTF.

- No differences in TTF or PFS between initial XRT or chemo
- TTF was 42.7 months for initial XRT and 43.8 months for the chemo arms
- Outcomes similar for AO and AOA

Multivariate Cox regression analysis of prognostic factors for TTF showed that EOR, age<50, histology, IDH1 mutation and MGMT promoter methylation were significant

- IDH1 mutations were prognostic but not predictive of treatment response

Other considerations

- Recent retrospective analyses of glioma showing that tumors with combination of IDH mutation and 1p19q LOH have a good prognosis irrespective of tumor grade?
- Reclassification of glioma based on molecular cytogenetic parameters as opposed to histological criteria only.
- What about long term effects of treatment? Little prospective data on late toxicity or the cognitive function and quality of life of patients treated with radiation and chemotherapy or both
- Cognitive function and QOL measures need to be prospectively evaluated in our clinical trials.

Summary

- Identification of biologically relevant molecular/genetic subsets of glioma can convey prognostic information and guide individualization of therapy

- Clinical trials need to stratify based on molecular/genetic subsets mandating tissue acquisition and cooperative efforts. For anaplastic glioma, presence of IDH mutation and 1p19q status is an important predictive factor for benefit of chemotherapy.

- Role of IDH mutations and possible therapeutic implications need to be explored