High Grade Gliomas: Update in Treatment and Care
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Objectives

• Provide updates on classification of high grade gliomas
• Demonstrate the importance of molecular classification
• Review standard treatment of high grade gliomas
• Give an overview of new and emerging treatments
High Grade Gliomas

**Pathologic classification**
- Glioblastoma (Grade IV astrocytoma)
- Anaplastic astrocytoma (Grade III astrocytoma)
- Anaplastic oligodendroglioma (Grade III oligodendroglioma)
- Mixed anaplastic oligoastrocytoma (Grade III)

**Molecular Classification**
- MGMT methylation
- IDH1
- 1p/19q
- Others
High Grade Gliomas: Molecular Classification

MGMT (O-6-methylguanine DNA methyltransferase)

- Methylated or unmethylated
- Methylated = Better prognosis/response to treatment
- Methylated MGMT confers less repair to Temozolomide
- 40% of GBM have methylated MGMT
High Grade Gliomas: Molecular Classification

**IDH1 (Isocitrate dehydrogenase 1)**
- Mutated or wild type (wt) (unmutated)
- Mutated=better prognosis
- Mechanism not understood
- Anaplastic astrocytoma IDH1 wt may be similar to GBM
- Low grade tumors often have IDH1 mutation

**1p/19q (chromosomal co-deletion)**
- Only seen in oligodendroglioma
- Co-deleted or intact (non-deleted)
- Co-deleted=better prognosis/response to treatment
- Co-deleted often have dramatic response to chemotherapy
Future Changes in Classification

**High risk glioma**
- GBM with wild type IDH1
- AA, AO, AOA with wild type IDH1

**Medium risk glioma**
- GBM with IDH1 mutation
- AA, AO, AOA with IDH1 mutation
- Low grade glioma with wild type IDH1

**Low risk glioma**
- AO or AOA with IDH1 mutation and 1p/19q co-deletion
- Low grade glioma with IDH1 mutation
Future Changes in Classification

• Wide scale genomic sequencing will likely change the way tumors are classified and treated

• Genomic sequencing is currently available through research labs and private companies

• Not ready for prime time yet
Standard Treatments
Standard Treatments: Newly Diagnosed

**Glioblastoma (GBM)-Stupp Regimen**
- 6 weeks of radiation with concurrent temozolomide (Temodar)
- 6-12 cycles of Temodar after chemoradiation

**Anaplastic tumors (AA, AO, AOA)**
- No current standard treatment
- Two ongoing clinical trials-CODEL and CATNON
- Various combinations of radiation and chemotherapy
- IDH1 wild type AA-treat like GBM?
Recurrent High Grade Glioma

**Glioblastoma**
- Bevacizumab (Avastin)
- No longer used in newly diagnosed
- Given intravenously every 2 weeks

**AA/AO/AOA**
- No standard
- Radiation often given if not already (AO, AOA)
- Temodar given in dose dense regimen
- PCV (procarbazine, CCNU, vincristine)
- Avastin
- Surgery often done to confirm the pathology
New and Emerging Therapies
New and Emerging Therapies

- Targeted therapies
- Immunotherapies
- Overcoming resistance
- Viral therapies
- Future Directions
Targeted Therapies

• Target specific pathways that drive tumor growth
  – Vascular endothelial growth factor (VEGF)
  – Epidermal growth factor receptor (EGFR)

• Targeted therapies make up the majority of current clinical trials

• Many trials combine experimental drug with Avastin
Angiogenesis inhibition

- Avastin normalizes blood vessels
- Starves tumor of blood supply
- Many other drugs like Avastin in trials
Definitions

• 3 Phases of clinical trials
  – Phase I: Dose finding study of new drug
  – Phase II: Testing the drug at the established dose
  – Phase III: Randomized double blind study to determine effectiveness of drug and establish it as a new standard

• 2 Common designs
  – Randomized, placebo controlled
  – Open label: all patients receive the study drug
Targeted Therapy: Downstream Pathways

- PI3 kinase pathway
- Phase II trial of buparlisib recently reported
- Single agent activity in recurrent GBM disappointing
- Other PI3 kinase inhibitors in combinations will be launched
Immunotherapy (Vaccines)

- General principle is to stimulate the immune system to fight the tumor
- Many different mechanism and many trials
  - ICT-107-Phase II trial in newly diagnosed GBM
    ✓ Dendritic cells given with GBM peptides
    ✓ Demonstrated improvement in time to progression but not overall survival
  - ACT IV-Phase III trial in newly diagnosed GBM
    ✓ Antibodies to mutant EGFRvIII receptor
    ✓ Trial will be completed this year
  - DCVax-Phase III trial in newly diagnosed GBM
    ✓ Dendritic cells given with tumor lysate
    ✓ Phase II results promising
Immunotherapy: Checkpoint inhibitors

• GBM inhibits the immune system

• Regulatory T cells and PD1 inhibit immune response

• Inhibiting these pathways promotes immune response

• Similar efforts in melanoma
Immunotherapy: Checkpoint inhibitors

Phase 2 trial of various combinations of ipilimumab, nivolumab, and bevacizumab (Avastin) is enrolling
Overcoming Resistance

**Resistance to Temodar**

- PARP inhibition - PARP is a DNA repair pathway
- PARP repairs DNA damage from Temodar and radiation
- Phase II trial newly diagnosed MGMT methylated GBM will be enrolling soon

**Resistance to Avastin**

- Mediated through SDF1-CXCR4 pathway
- Plerifixator is a CXCR4 inhibitor
- Phase I study recently completed
Viral Therapies

• Virus is delivered directly to tumor through surgery
• Virus selectively affects tumor cells and not normal cells
• Several viruses have been tested
  – Adenovirus
  – Herpes simplex virus
  – Newcastle disease virus
  – Reovirus
  – Measles virus
  – Polio virus
Viral Therapies

A. Conditional replication
1: TSP
   - Off: tumor cell
   - On: cancer cell

2: Attenuation
   - Viral gene
   - Deletion mutation

   - Adenovirus: ONYX-15, E1AΔ24
   - HSV: ΔICP6, ΔICP34.56

3: Transductional targeting
   - Ad fiber HSV gD
   - Native receptor
   - Retargeted receptor overexpression in tumor cell

   - e.g., CRAd-survivin-pK7

4: Naturally smart oncolytic virus
   - Normal cell
   - PKR → PKR
   - Cancer cell
   - PKR → PKR
   - EGFR, Ras

   - e.g., Reovirus

B. Diagrams illustrating the process of viral therapy
C. Diagrams showing the targeting and replication of viral particles
D. Diagrams demonstrating the interaction with normal and cancer cells
E. Diagram showing the spread and inhibition of viral replication

Future Directions

• Genomic sequencing will become more practical
• This will lead to more individualized medicine
• Targeted drugs will be more precise
• Unmethylated MGMT patients will be treated differently
• Clinical trial design will change as tumor classification changes
• Better understanding of the host will lead to new treatments
THANK YOU
Any Questions?

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