Objectives

- Apply current standards of practice in the treatment of a patient with newly diagnosed Glioblastoma
- Discuss current standards of practice for management of recurrent Glioblastoma
- Identify common complications for a patient with a Glioblastoma

Glioblastoma Multiforme

- 23,130 will be diagnosed with a malignant tumor of the brain or spinal cord
- An estimated 14,080 will die from those tumors
- American Society, 2013
- Glioblastoma multiforme (GBM) is the most common and aggressive
- Median survival is ~15 months
- Most recur within 9 months

Case Study: Newly diagnosed glioblastoma

LP, 58 year old white male presents to his PCP with the following complaints:

1. 1 month history of headaches
2. Decreased sensitivity to smell and taste
3. Progressive left sided weakness
4. Diminished motor dexterity in left hand

ROS: positive for decreased smell and taste and change in balance; additionally family noted slower speech and dragging left foot

PE: positive for slow speech, left facial droop, pronator drift of left arm, unable to touch nose with eyes closed with left hand
Case Study

Imaging - glioma

Resection not feasible
Stereotactic biopsy OR Open biopsy
Subtotal resection
Maximal resection
Resection + carmustine wafer

Case Study

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Imaging - glioma

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Glioblastoma

KPS $\geq 60$

$\leq 70$: RT + TMZ

RT / chemotherapy / Palliative care

KPS < 60

>70: RT + TMZ

Follow up

MRI 2-6 weeks after Radiation

Then every 2-4 months for 2-3 years

Less frequently after 3 years

Goals

Diagnosis

Maximal tumor resection

Alleviation of symptom
Treatment: Surgery

- Types:
  - Stereotactic biopsy
  - Open biopsy
  - Debulking
  - Total resection
  - Chemotherapy wafer implants

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Goal:
- Destroy tumor cells without injuring normal cells
- Reduce or stabilize size of tumor after surgery
- Fractionated EBRT (external beam radiation therapy)
- Standard adjuvant therapy
- Typical dose = 60 Gy, given in 1.8-2.0 Gy, 5 days/week for 6 weeks


**Treatment: Radiation Therapy**

- Side Effects:

<table>
<thead>
<tr>
<th>Acute</th>
<th>Early delayed</th>
<th>Late</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scalp erythema</td>
<td>Somnolence</td>
<td>Radiation necrosis</td>
</tr>
<tr>
<td>Cerebral edema</td>
<td>Neuro deficits</td>
<td>Dementia</td>
</tr>
<tr>
<td>Seizures</td>
<td>Fatigue</td>
<td>Cognitive function</td>
</tr>
<tr>
<td>Headache</td>
<td></td>
<td>Leukoencephalopathy</td>
</tr>
<tr>
<td>N &amp; V</td>
<td></td>
<td>New neoplasm</td>
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<tr>
<td>Fatigue</td>
<td></td>
<td>Fatigue</td>
</tr>
</tbody>
</table>

**Treatment: Chemotherapy**

- Implanted wafer
  - Carmustine biodegradable wafer
  - Placed at time of initial or recurrent surgery
  - Released immediately and lasts for several weeks


- Westphal et al.
  - 240 patients randomized to either carmustine wafer or placebo
  - Groups similar for age, sex, KPS and tumor histology
  - Median survival: 13.9 months vs 11.6 months
  - Adverse effects comparable except:
    - CSF leak: 5% carmustine vs 0.8% placebo;
    - Intracranial hypertension: 9.1% carmustine vs 1.7% placebo

Treatment: Chemotherapy

- Temozolomide (TMZ)
  - Standard of care
  - Alkylating agent
  - Crosses the blood brain barrier


Treatment: Chemotherapy

- Temozolomide
  - Peak level at 1.2 hours
  - Half-life 1.9 hours
  - Dosing
    - Concurrent with RT: 75mg/m$^2$ per day for 42 days
    - Adjuvant: given for 5 days of each 28 day cycle
      - Dose of first cycle = 150mg/m$^2$ for 5 days
      - Cycles 2-6: 200mg/m$^2$ for 5 days

Treatment: Chemotherapy

- Temozolomide
  - Side Effects:
    - Dose limiting: myelosuppression- neutropenia, thrombocytopenia
    - Thromboembolism
    - Fatigue
    - Pneumonia
    - Nausea/vomiting
    - Rash
    - Constipation
    - Arthralgias

Treatment: Chemotherapy

- Yung and colleagues:
  - Phase II trial for recurrent GBM
  - Randomized 225 patients
  - Improved survival with TMZ vs procarbazine


Treatment: Chemoradiation

- Stupp and colleagues
  - Phase III study for newly diagnosed GBM
  - 573 patients from 85 centers
  - Randomized to either RT alone or RT plus TMZ
  - Median survival: 14.6 months RT + TMZ vs 12.1 months in the RT group
  - 2 year survival: 26.5% for the RT + TMZ group vs 10.4% RT group
  - 5 year survival: 9.8% vs 1.9%


Case Study: Recurrence
Case Study

- LP had a sub-total resection of his glioblastoma. He completed fractionated EBRT with concurrent and adjuvant TMZ.
- His initial MRI 4 weeks after RT is clear of tumor. He continues taking the temozolomide.
- MRI at 12 months shows a recurrence.

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Diffuse

- Palliative
- Systemic Chemo / Surgery
- Alternating electric field therapy

Local

- Resectable +/- wafer
- Palliative
- Systemic chemo OR Radiation
- Alternating electric field therapy

Unresectable
Virtually all relapse
No standard of care for relapse
Pseudoprogression

Re-resection
- Studies have shown re-resection to increase survival time
- Patient bias - high functional status, tumor location, minimal medical contraindications

Chemotherapy-impregnated wafers:
- double-blind, randomized study
- 6 month survival 64% with wafer vs 44% with placebo
Bevacizumab
- Monoclonal antibody for VEGF-A (vascular endothelial growth factor A)
- Inhibits proliferation of endothelial cells and angiogenesis
- Side effects:
  - Intracranial hemorrhage
  - Thrombotic events- DVT, PE and ischemic stroke
  - Hypertension
  - Impaired wound healing


Recurrent Disease
- Bevacizumab
  - May used alone or in combination with chemotherapy

<table>
<thead>
<tr>
<th></th>
<th>6 month progression free survival</th>
<th>Overall survival</th>
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<tbody>
<tr>
<td>Bevacizumab (n=85)</td>
<td>42.6%</td>
<td>9.2</td>
</tr>
<tr>
<td>Bevacizumab + irinotecan (n=82)</td>
<td>50.3%</td>
<td>8.7</td>
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Recurrent Disease
- Temozolomide rechallenge
  - Perry et al conducted a phase II study to assess the efficacy and safety of continuous dose-intense TMZ
  - 91 patients who progressed after standard treatment
  - Divided into groups according to when they progressed
    - Early: progression before completion of 6th cycle
    - Extended: progression after 6th cycle but before end of adjuvant
    - Rechallenge: progression after adjuvant and treatment free > 2 months
  - Received TMZ 50mg/m² per day up to a year or until progression

Recurrent Disease

Results of RESCUE study


Re-irradiation

- Local recurrence: single fraction or fractionated stereotactic radiation


Treatment: Alternating Electric Field Therapy

- Approved by FDA in 2011

- Delivers alternating low-intensity and intermediate frequency electrical fields to a tumor

- The electrical fields cause apoptosis
Clinical trial by Stupp et al.
237 patients randomized either to best standard chemotherapy or to electric field therapy
Median survival: 6.6 vs 6.0 months

Best result if worn for at least 18hrs/day
Decreased adverse effects
Most common: scalp irritation
QOL favored electric field therapy

Case Study: Complications of Glioblastoma
Case Study

- LP opted for a re-resection, continued with temozolomide and started alternating electric field therapy. He started back to work part time as a college professor and was doing some traveling with family.
- His symptoms have mostly subsided, being replaced with fatigue.
- Experienced his first seizure and presented to the local ED.

Complications: Seizures

- If witnessed: keep patient safe, assess movement, time
- Anti-epileptic drugs (AEDs)
  - Seizure prophylaxis is not recommended; may consider perioperatively
  - First generation drugs: phenytoin, phenobarbital should be avoided due to effects on metabolism
  - Newer agents: levetiracetam, topiramate, valproic acid

Complications: Thrombosis

- Hypercoagulability
  - Risk for DVT/PE
  - Risk for hemorrhage into tumor
  - Anticoagulation: low molecular weight heparin
### Complications: Progression

- Signs & symptoms depend on location of tumor
  - Manage the symptoms
  - Treat the underlying cause vs palliative care

### Supportive Care: Corticosteroids

- Dexamethasone
  - Tumor-associated edema
  - 24 hours before RT when extensive mass effect present
  - Lowest dose possible for shortest time possible
  - Monitor blood glucose
  - \(H_2\) blockers or proton pump inhibitors for GI prophylaxis

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### Conclusion

- Newly diagnosed GBM
  - Maximal resection with/out carmustine wafer
  - Radiation with concurrent and adjuvant temozolomide

- Recurrent GBM
  - Re-resection with/out carmustine wafer
  - Bevacizumab
  - Rechallenge with temozolomide
  - Re-irradiation
  - Alternating electric field therapy
Thank You

To learn more about Ohio State's cancer program, please visit cancer.osu.edu or follow us in social media: