Positive Quality Intervention: Temozolomide (Temodar®) for Glioblastoma Multiforme

Description: The purpose of this PQI is a summary of the process for initiating and monitoring oral temozolomide therapy in patients with Glioblastoma Multiforme (GBM).

Background: Temozolomide is indicated in newly diagnosed GBM concomitantly with radiotherapy and then as maintenance treatment, in anaplastic astrocytoma, and is used off-label in a number of other indications. GBM is the most common primary malignant brain tumor in adults and comprises 54% of all gliomas with a median survival of 6 to 12 months. Temozolomide is an FDA approved medication used to treat GBM. Temozolomide is a prodrug that is converted into its active alkylating metabolite which causes DNA double strand breaks and apoptosis. Concurrent treatment with temozolomide and radiation followed by a 4 week break, then maintenance temozolomide for 5 days every 28 days for 6 cycles was found to improve 2 year survival from 10.4% (radiation alone) to 26.5% (radiation + temozolomide). Furthermore, patients with MGMT promoter methylated GBM were shown to have a better 18-month overall survival with concurrent temozolomide and radiation (62%) when compared with unmethylated MGMT (8%).

PQI Process:

- Screen for Hepatitis B and C prior to starting treatment
  - Initiate entecavir or tenofovir for history of hep B infection to prevent reactivation
- Ensure appropriate indication and dose, keeping in mind that dose modifications occurred frequently in the clinical trials
  - Temozolomide 75 mg/m² PO daily during radiation followed by a 4 week break, then 150-200 mg/m² PO daily x 5 every 28 days for 6 cycles
- Concurrent temozolomide with radiation can cause lymphocytopenia therefore ensure appropriate prophylaxis of Pneumocystis Jiroveci with oral trimethoprim-sulfamethoxazole, inhaled pentamidine, atovaquone or dapsone and should be continued until recovery from lymphocytopenia (lymphocyte count at or greater than 0.8 x 10⁹/L)
- 5HT3 antagonist should be prescribed for prevention and treatment of nausea and vomiting
  - Recommend 5HT3 antagonist 30 to 60 minutes prior to temozolomide for prevention of nausea and vomiting
- Monitor pregnancy, CBC (thrombocytopenia, neutropenia, lymphopenia), liver enzymes, pneumocystis

Dosing Interruption or Discontinuation during Concomitant Radiotherapy and Temozolomide

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Therapy Interruption</th>
<th>Discontinue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute Neutrophil Count</td>
<td>≥ 0.5 x 10⁹/L and &lt; 1.5 x 10⁹/L</td>
<td>&lt; 0.5 x 10⁹/L</td>
</tr>
<tr>
<td>Platelet Count</td>
<td>≥ 10 x 10⁹/L and less &lt; 100 x 10⁹/L</td>
<td>&lt; 10 x 10⁹/L</td>
</tr>
<tr>
<td>Common Toxicity Criteria (CTC) Non-Hematological Toxicity (except for alopecia, nausea, vomiting)</td>
<td>CTC Grade 2</td>
<td>CTC Grade 3 or 4</td>
</tr>
</tbody>
</table>

Temozolomide Dose Levels for Maintenance Treatment

<table>
<thead>
<tr>
<th>Dose level</th>
<th>Dose (mg/m²/day)</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>-1</td>
<td>100</td>
<td>Reduction for prior toxicity</td>
</tr>
<tr>
<td>0</td>
<td>150</td>
<td>Dose during Cycle 1</td>
</tr>
<tr>
<td>1</td>
<td>200</td>
<td>Dose during Cycles 2-6 in absence of toxicity</td>
</tr>
</tbody>
</table>

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Temozolomide Dose Reduction or Discontinuation during Maintenance Treatment

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Reduce Temozolomide by 1 Dose Level</th>
<th>Discontinue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute Neutrophil Count</td>
<td>Less than $1.0 \times 10^9$/L</td>
<td>Discontinue if dose reduction to $&lt; 100$ mg/m$^2$ is required or if the same Grade 3 non-hematological toxicity (except for alopecia, nausea, vomiting) recurs after dose reduction</td>
</tr>
<tr>
<td>Platelet Count</td>
<td>Less than $50 \times 10^9$/L</td>
<td></td>
</tr>
<tr>
<td>CTC Non-Hematological Toxicity (except for alopecia, nausea, vomiting)</td>
<td>CTC Grade 3</td>
<td>CTC Grade 4</td>
</tr>
</tbody>
</table>

Temozolomide Dose Modification Table

150 mg/m$^2$/day x 5 days (Starting Dose) or 200 mg/m$^2$/day x 5 days → Measure Day 22 ANC and platelets

Measure ANC and platelets on Day 29 (Day 1 of next cycle)

Based on lowest counts at either Day 22 or Day 29

ANC less than 1000/µL or platelets less than 50,000/µL → Hold until ANC > 1500/µL and platelets > 100,000/µL; reduce dose by 50 mg/m$^2$/d for subsequent cycle

ANC 1000/µL - 1500/µL or platelets 50,000/µL - 100,000/µL → Hold until ANC > 1500/µL and platelets > 100,000/µL; maintain previous dose

ANC > 1500/µL and platelets > 100,000/µL → Increase dose to, or maintain dose at, 200 mg/m$^2$/d x 5d for subsequent cycle

Patient-Centered Activities:
- Provide Oral Chemotherapy Education (OCE) Sheet
- Provide Treatment Support Kit (TSK)
- Counsel patient on disease state, treatment regimen, what to expect and verify patient understanding
- Counsel patient on common side effects which include alopecia, constipation, nausea/vomiting, headache, and fatigue
- Temozolomide may be taken on an empty stomach 1-2 hours before radiation or at bedtime
- Counsel patient to swallow capsules (may be multiple) whole with a full glass of water
  - May administer on an empty stomach and/or bedtime to reduce nausea/vomiting and consistently take in this manner
  - Do not repeat dose if vomiting occurs after the dose is administered

References:
1. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Central Nervous System Cancers.
2. Temozolomide [prescribing information].