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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.[1] Temozolomide is an FDA approved medication used to treat GBM.[2] Temozolomide is a prodrug that is converted into its active alkylating metabolite which causes DNA double strand breaks and apoptosis.[2] 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).[3] 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%).[4]

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/m^2 PO daily during radiation followed by a 4 week break, then 150-200 mg/m^2 PO daily x 5 every 28 days for 6 cycles[2]
- Concurrent temozolomide with radiation can cause lymphocytopenia therefore ensure appropriate prophylaxis of Pneumocystis Jiroveci with oral trimethoprim-sulfamethoxazole, inhaled pentamidine, atovaquone or dapsone[2] and should be continued until recovery from lymphocytopenia (lymphocyte count at or greater than 0.8 x 10^9/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[2]

Dosing Interruption or Discontinuation during Concomitant Radiotherapy and Temozolomide[2]

Toxicity	Therapy Interruption	Discontinue
Absolute Neutrophil Count	≥ 0.5 x 10^9/L and < 1.5 x 10^9/L	< 0.5 x 10^9/L
Platelet Count	≥ 10 x 10^9/L and less < 100 x 10^9/L	< 10 x 10^9/L
Common Toxicity Criteria (CTC) Non-Hematological Toxicity (except for alopecia, nausea, vomiting)	CTC Grade 2	CTC Grade 3 or 4

Temozolomide Dose Levels for Maintenance Treatment[2]

Dose level	Dose (mg/m^2/day)	Remarks
-1	100	Reduction for prior toxicity
0	150	Dose during Cycle 1
1	200	Dose during Cycles 2-6 in absence of toxicity

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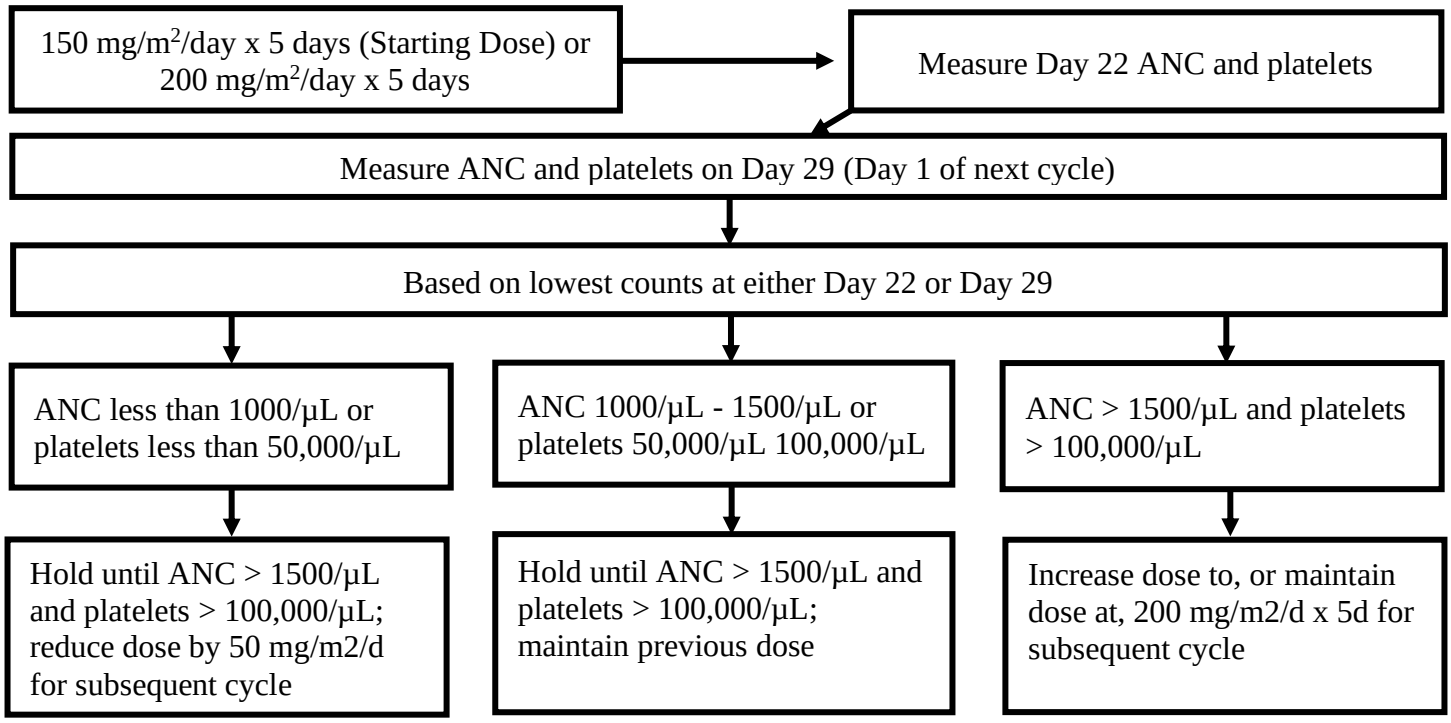
Temozolomide Dose Reduction or Discontinuation during Maintenance Treatment[2]

Toxicity	Reduce Temozolomide by 1 Dose Level	Discontinue
Absolute Neutrophil Count	Less than 1.0 x 10^9/L	Discontinue if dose reduction to < 100 mg/m^2 is required or if the same Grade 3 non-hematological toxicity (except for alopecia, nausea, vomiting) recurs after dose reduction
Platelet Count	Less than 50 x 10^9 /L	
CTC Non-Hematological Toxicity (except for alopecia, nausea, vomiting)	CTC Grade 3	CTC Grade 4

Temozolomide Dose Modification Table[2]



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].
3. Stupp R, Mason WP, van den Bent MJ, et al: Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 352:987-96, 2005.
4. Hegi ME, Diserens AC, Godard S, et al: Clinical trial substantiates the predictive value of O-6- methylguanine-DNA methyltransferase promoter methylation in glioblastoma patients treated with temozolomide. Clin Cancer Res 10:1871-4, 2004.