SACT PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

Temozolomide with Concomitant Radiotherapy

PROTOCOL REF: MPHATEMCR
(Version No. 1.3)

Approved for use in:

Adult patients with newly-diagnosed glioblastoma multiforme concomitantly with radiotherapy and subsequently as monotherapy treatment (see separate protocol)

Dosage:

Concomitant TMZ with Radiotherapy

Drug	Dose	Route	Frequency
Temozolomide	75mg/m^2	Oral	Daily for 42 days

Followed by temozolomide monotherapy (see separate protocol), to be reviewed by oncologist 4 weeks after completion of radiotherapy.

Drug	Dose	Route	Frequency
Temozolomide	150mg/m^2	Oral	Once daily for 5 days At Cycle 2, the dose is escalated to 200 mg/m2, if tolerated, for up to 12 cycles

Supportive treatments:

- Ondansetron 8mg – One hour before chemotherapy
- Cyclizine 50mg Tablets – 50mg up to three times a day when required

Additional Medication:

PCP prophylaxis – co-trimoxazole 960mg PO once a day on Mondays, Wednesdays and Fridays of each week, which should continue for 4 weeks after last cycle, or until lymphocyte counts return to normal values.

Emetogenic risk:

Mildly emetogenic.

Extravasation risk:

Not applicable

Administration:

Day	Drug	Dose	Route	Frequency
1-21	**Temozolomide**	**75mg/m^2**	**Oral**	**30 minutes before radiotherapy (or on the morning at weekends) for 21 days**
22-42	**Temozolomide**	**75mg/m^2**	**Oral**	**30 minutes before radiotherapy (or on the morning at weekends) for 21 days**
1 to 70	**Co-trimoxazole**	**960mg**	**Oral**	**Mondays, Wednesdays and Fridays during treatment and for up to 4 weeks after completion of treatment**

Temozolomide capsules are to be swallowed whole with a glass of water on an empty stomach, 1 hour before or after meals. Temozolomide capsules should be taken 30 minutes prior to the radiotherapy and in the morning at weekends (non-radiotherapy days).

Once the radiotherapy is completed, there will be a 4 week treatment free period before the adjuvant cycle commences.

For patients unable to swallow capsules, please refer to the information sheet produced by Great Ormond Street Hospital for instructions on how to produce a mixture (available at https://www.gosh.nhs.uk/medical-information-0/medicines-information/temozolomide)

Main toxicities:

Temozolomide		
System Organ Class	Frequency	
Infections and infestations	Common	Infections, herpes zoster, pharyngitis, candidiasis oral, Pneumocystis carinii pneumonia
Blood and lymphatic system disorders	Common	Febrile neutropenia, neutropenia, thrombocytopenia, lymphopenia, leukopenia, anaemia
Immune system disorders	Common	Allergic reaction

Endocrine disorders	Common	Cushingoid
Metabolism and nutrition disorders	Very common	Anorexia
	Common	Hyperglycaemia
Psychiatric disorders	Common	Agitation, amnesia, depression, anxiety, confusion, insomnia
Nervous system disorders	Very common	Convulsions, hemiparesis, aphasia/dysphasia, headache
	Common	Ataxia, balance impaired, cognition impaired, concentration impaired, consciousness decreased, dizziness, hypoesthesia, memory impaired, neurologic disorder, neuropathy, paraesthesia, somnolence, speech disorder, taste perversion, tremor
Eye disorders	Common	Hemianopia, vision blurred, vision disorder, visual field defect, diplopia, eye pain
Ear and labyrinth disorders	Common	Deafness, vertigo, tinnitus, earache
Vascular disorders	Common	Haemorrhage, embolism pulmonary, deep vein thrombosis, hypertension
Respiratory, thoracic and mediastinal disorders	Common	Pneumonia, dyspnoea, sinusitis, bronchitis, coughing, upper respiratory infection
Gastrointestinal disorders	Very common	Diarrhoea, constipation, nausea, vomiting
	Common	Stomatitis, abdominal pain, dyspepsia, dysphagia
Skin and subcutaneous tissue disorders	Very common	Rash, alopecia
	Common	Erythema, dry skin, pruritus
Musculoskeletal and connective tissue disorders	Common	Myopathy, muscle weakness, arthralgia, back pain, musculoskeletal pain, myalgia
Renal and urinary disorders	Common	Micturition frequency, urinary incontinence
General disorders and administration site conditions	Very common	Fatigue

	Common	Fever, influenza-like symptoms, asthenia, malaise, pain, oedema, oedema peripheral
Investigations	Common	Liver enzymes elevation, weight decreased, weight increased

Listed above are the common toxicities associated with temozolomide. For a comprehensive list of toxicities please refer to the SPC: Temozolomide 20 mg hard capsules - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)

Interactions:

No studies have been conducted to determine the effect of temozolomide on the metabolism or elimination of other medicinal products. However, since temozolomide does not undergo hepatic metabolism and exhibits low protein binding, it is unlikely that it would affect the pharmacokinetics of other medicinal products. Please refer to SPC for further details: Temozolomide 20 mg hard capsules - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)

Investigations and treatment plan:

	Pre	Week 1	Week 2	Week 3	Ongoing
Informed Consent	x				
Radiographer / Nursing assessment	x	x	x	x	Every week
SACT Assessment (to include PS and toxicities)	x	x	x	x	Every cycle
FBC	x	x	x	x	Once a week
U&E & LFTs	x	x	x	x	Once a week
MRI scan	x				As clinically indicated
Weight recorded	x	x	x	x	Every week
Height recorded	x				

Dose Modifications and Toxicity Management:

Haematological toxicity:

During treatment a complete blood count should be obtained weekly. If radiotherapy is interrupted, continue temozolomide (maximum 49 days total).

Toxicity	Temozolomide interruption	Temozolomide discontinuation
ANC Platelet count	≥ 0.5 and ≤ 1.5 x 10^9 /L ≥ 10 and ≤ 99 x 10^9 /L	< 0.5 x 10^9/L < 10 x 10^9/L
Non-haematological toxicity (except for alopecia, nausea, vomiting)	Grade 2	Grade 3 or 4

Dosing in renal and hepatic impairment:

Renal impairment

No dose adjustment necessary

Hepatic toxicity

Review concurrent medication (particularly anticonvulsants) and consider their effect on liver function. No dose adjustments necessary for mild to moderate hepatic impairment. No date available for patients with severe hepatic impairment. Stop temozolomide if there is a progressive rise in transaminases or rise in bilirubin

Marrow aplasia

If thrombocytopenia continues after discontinuation of temozolomide with reduction in neutrophil count, then:

- Stop co-trimoxazole
- Repeat FBC daily
- Add daily filgrastim
- Supportive blood product transfusions as necessary
- Contact haematologists for advice in severe cases

References:

1. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma Stupp R et al NEJM 2005 352:987-996
2. National Institute for Health and Care Excellence (NICE) TA 121. Carmustine implants and temozolomide for the treatment of newly diagnosed high-grade glioma. Last updated March 2014.
3. Temozolomide 20mg hard capsules, summary of product characteristics, Ranbaxy (UK) Limited a Sun Pharmaceutical Company. Available at: Temozolomide 20 mg hard capsules - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) Last updated 15/03/2023.
4. Supplement to: Krens S D, Lassche, Jansman G F G A, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. *Lancet Oncol* 2019; 20: e201–08.

Circulation/Dissemination

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Version History

Date	Vesion	Author name and designation	Summary of main changes
As of 6th April 2023	V 1.3	**Hugh O'Neill**	Updated format to new CCC template