Systemic Anti Cancer Therapy Protocol

RMP (Rituximab, Methotrexate and Procarbazine) Primary CNS Lymphoma

PROTOCOL REF: MPHARMPHA
(Version No.3.0)

Approved for use in:

Primary CNS lymphoma - for patients considered unsuitable for more intensive chemotherapy.

Dosage:

Cycle 1 and 4 (Induction)

Drug	Dose	Route	Frequency
Rituximab	**375mg/m^2**	IV infusion	Day 1
Methotrexate	**3000mg/m^2**	IV infusion	Day 2 (split into 300mg/m^2 over 15 minutes and then 2700mg/m^2 over 3 hours)
Procarbazine	**60mg/m^2**	PO	Days 3 – 12 (50mg capsules only)

Cycle 2 & 3 and 5 & 6 (Induction)

Drug	Dose	Route	Frequency
Rituximab	**375mg/m^2**	IV infusion	Day 1,
Methotrexate	**3000mg/m^2**	IV infusion	Day 2, (split into 300mg/m^2 over 15 minutes and then 2700mg/m^2 over 3 hours)

Cycle length every 14 days (2 weeks) for 6 cycles (12 weeks in total)

NB: The nationally recognised protocol is a 42 day cycle with dosing every 2 weeks. To ensure safe electronic prescribing at CCC each treatment dose has been built as an individual cycle. This is reflected in this protocol.

Cycle 7 to 12 (Maintenance – start 2 weeks after last rituximab dose)

Drug	Dose	Route	Frequency
Procarbazine	**100mg**	**PO**	**OD on days 1 to 5 only (28 day cycle)**

Administration:

- Co-trimoxazole and PPIs **must be stopped at least 2 days prior to treatment**
- Piperacillin/Tazobactam (Tazocin®) should be avoided and meropenem used as first line treatment for febrile neutropenia following methotrexate infusion until methotrexate has cleared (level <0.1micromol/L)
- Due to the long retention time of rituximab in B cell depleted patients, women of childbearing potential should use effective contraceptive methods during and for 12 months following treatment with rituximab.
- The hydration fluids on day 2 **MUST** start at least 6 hours prior to the methotrexate infusion.
- The patient's urine pH **MUST** be >7 before the methotrexate infusion is started.
- If urinary pH <7 during methotrexate infusion then additional sodium bicarbonate 8.4% 50mL can be infused separately by slow IV infusion (to be prescribed prn in Meditech).
- The second methotrexate infusion **MUST** start immediately after the loading dose.
- The blood sample needs to be sent to Alder Hey hospital in a taxi and then the lab at Alder Hey need to be rung for the result which should be documented in the medical notes.
- Folinic acid (calcium folinate) should be started 24 hours after the **start** of the methotrexate infusion
- The first methotrexate level should be taken 48 hours after the **start** of the methotrexate infusion. The methotrexate level should then be repeated daily until it is <0.1micromol/L at which point folinic acid rescue can stop.
- The dose of folinic acid (calcium folinate) may need to be modified 48 hours after the start of the methotrexate infusion in response to methotrexate levels (see High Dose Methotrexate Overview Protocol)
- If the serum creatinine increases by more than 25% from baseline then the folinic acid rescue should be escalated even before methotrexate level is known – seek urgent consultant advice.

- If severe methotrexate toxicity is suspected, then seek early consultant advice regarding the use of recombinant glucarpidase.
- Take procarbazine with food to avoid nausea
- Maintenance procarbazine should only be started if there is at least a partial response to induction treatment

Anti-emetic risk:

Severely emetogenic.

Supportive treatments:

Rituximab pre-infusion medicines:

- Paracetamol PO 1g
- Chlorphenamine IV bolus 10mg
- Hydrocortisone sodium succinate IV bolus 100mg

High dose methotrexate pre-infusion medicines:

- Hydration fluids to start at least 6 hours before methotrexate
- Sodium bicarbonate 1g PO four times daily from 24 hours pre-methotrexate
- Sodium bicarbonate 8.4% IV 50mL slow IV bolus prn (to be used if urinary pH <7)

Induction treatment supportive medicines:

- Allopurinol PO 100mg or 300mg daily (depending on renal function) for first cycle
- Aciclovir 400mg PO twice daily
- Famotidine 20mg twice daily (only if on existing PPI therapy, not needed routinely)
- Filgrastim SC 30 or 48 million units OD in cycles 2 and 5 only from days 4 to 10 (30million units if <70kgs and 48 million units >70kgs).
- Fluconazole PO 100mg daily
- Folinic acid IV 60mg every 6 hours to start 24 hours after the *start* of methotrexate infusion. See administration advice for further information.
- Ondansetron PO 8mg twice daily days 2 to 4.
- Pentamidine NEB 300mg every 28 days OR atovaquone liquid PO 750mg BD

Suspend co-trimoxazole and routine folic acid until methotrexate level <0.1micromol/L

Maintenance treatment supportive medicines:

- Co-trimoxazole PO 480mg OD
- Ondansetron PO 8mg BD for 5 days

Extravasation risk:

Rituximab: non-vesicant

Methotrexate: non-vesicant

Refer to the network guidance for the prevention and management of extravasation

Interactions:

Methotrexate - see High Dose Methotrexate Overview Protocol

Procarbazine

Procarbazine is a weak MAO inhibitor and therefore can interact with certain food and drugs. Avoid alcohol, alcohol-free beers, wines, mature cheeses, salami, yeast or beef extracts during procarbazine treatment.

Treatment schedule (Induction):

Day	Drug	Dose	Route	Diluent and rate
1	**Paracetamol**	**1g**	**PO**	
	Chlorphenamine	**10mg**	**IV**	Bolus dose over 3-5 minutes
	Hydrocortisone	**100mg**	**IV**	Bolus dose over 3-5 minutes
	Rituximab	**375mg/m^2**	**IV**	**Non-Hodgkin patients ONLY.** **≤450mg** 250mL sodium chloride 0.9% **≥500mg** 500mL sodium chloride 0.9% Rate as per rituximab infusion guideline.
2	**Ondansetron**	**8mg**	**IV**	Infuse over 15 minutes
	IV hydration: **1L sodium chloride 0.18% / glucose 4% containing 20mmol potassium chloride and 50ml 8.4%sodium bicarbonate (bicarbonate to be added on the ward)**		**IV**	Start infusion 6 hours prior to methotrexate infusion, run at a rate of 250ml/hr for 6 hours, then run at a rate of 125ml/hr for 3 hours 15 minutes concurrent with methotrexate infusions, then run at a rate of 250ml/hr until desired methotrexate level is achieved (<0.1microlmol/l).
	Methotrexate	**300mg/m^2**	**IV**	In 100mls Sodium Chloride 0.9% over 15 minutes.

				The patient's urinary pH MUST be >7 before starting the infusion.
	Methotrexate	**2700mg/m^2**	**IV**	In 1000mls of Sodium Chloride 0.9% over 3 hours.
3 to12 **(cycle 1 & 4 only)**	**Procarbazine**	**60mg/m^2**	**PO**	Round to nearest 50mg

Treatment schedule (maintenance):

Day	Drug	Dose	Route	Diluent and rate
1 to 5	**Procarbazine**	**100mg**	**PO**	Once daily

Main toxicities:

Thrombocytopenia, neutropenia, anaemia, nausea, vomiting, diarrhoea and infusion related reactions.

Glucarpidase – Methotrexate reversal agent

NHS England will fund glucarpidase as a reversal agent for methotrexate (unlicensed in UK) for adults receiving high-dose methotrexate chemotherapy (doses >1g/m^2)

- Who develop significant deterioration in renal function (>1.5x ULN and rising, or the presence of oliguria) OR
- Have toxic plasma methotrexate level AND
- Have been treated with all standard rescue and supportive measures AND
- At risk of life-threatening methotrexate-induced toxicities

The recommended dose is one single intravenous injection of 50units/kg

Refer to CCC glucarpidase protocol for further information

Investigations and treatment plan:

	Pre	All cycles Day 1	All cycles Day 4	Ongoing
Informed Consent	X			
Clinical Assessment	X	X		
SACT Assessment (including PS and toxicity assessment)	X	X		
FBC	X	X		
U&E & LFTs & Magnesium	X	X		
CrCl (Wright)	X	X		
MRI scan	X			At the end of treatment and if clinically indicated
CSF analysis	X			
ECG				If clinically indicated
Blood pressure	X	X		Continuous monitoring required if on Rituximab
Temperature, respiratory rate, pulse		X		Continuous monitoring required if on Rituximab
Methotrexate levels			X	Repeat daily until cleared
Weight	X	X		
Height	X			
Hepatitis B core antibody and surface antigens & Hep C & HIV 1+2	X			
Blood glucose	X			Repeat if clinically indicated
Pregnancy test	X			If clinically indicated

Dose Modifications and Toxicity Management:

Haematological toxicity:

Treatment can proceed if-

ANC ≥ 1.5 x 10^9/L	Platelets ≥ 100 x 10^9/L

Note therapy can proceed if values are below these levels if cytopenias known to be secondary to disease.

If counts are below above values then RMP should be delayed for a maximum 2 weeks (thereafter chemo will need to be discontinued).

These haematological guidelines assume that patients are well with good performance status, that other acute toxicities have resolved and the patient has not had a previous episode of neutropenic sepsis.

Non Haematological Toxicity:

Dosing in renal and hepatic impairment:
A fluid space, e.g. pleural effusion or ascites, is potentially very dangerous as methotrexate can accumulate and cause prolonged toxicity. High dose methotrexate should not be given in such cases.

Methotrexate			
Renal, CrCl (ml/min) – use Wright equation			
>60		100% dose	
40-60		50%	
<40		Omit	
Hepatic			
Bilirubin (micromol/L)		ALT (units/L)	Dose modification
<50	and	<180	100% dose
50-84	or	≥180	75% dose
≥85			Omit
Procarbazine			
Renal, CrCl (ml/min) – use Wright equation			
>10		100% dose	

<10 or haemodialysis	Not recommended
Hepatic	
No dose adjustments needed. Use with caution in severe impairment (contraindicated).	

Infusion Related Reactions:

Non-Haematological toxicities:	
Rituximab	
Infusion-related Reactions	Severe infusion-related reactions with fatal outcome can have an onset ranging within 30 minutes to 2 hours after starting the first rituximab infusion. They can be characterised by pulmonary events and in some cases included rapid tumour lysis and features of tumour lysis syndrome (TLS) in addition to fever, chills, rigors, hypotension, urticaria, and angioedema. Severe cytokine release syndrome may occur. Monitor patients closely. Patients who develop evidence of severe reactions, especially severe dyspnea, bronchospasm or hypoxia should have infusion interrupted immediately. The patient should then be evaluated for evidence of TLS including appropriate laboratory tests and, for pulmonary infiltration, with a chest x-ray. The infusion should not be restarted until complete resolution of all symptoms, and normalisation of laboratory values and chest x-ray findings. At this time, the infusion can be initially resumed at not more than one-half the previous rate. If the same adverse reaction occurs for a second time, the decision to stop the treatment should be seriously considered on a case-by-case basis. Anaphylactic and other hypersensitivity reactions may occur. In contrast to cytokine release syndrome, true hypersensitivity reactions typically occur within minutes after starting infusion. Mild or moderate infusion-related reactions usually respond to a reduction in the rate of infusion. The infusion rate may be increased upon improvement of symptoms

References:

1. https://www.medicines.org.uk/emc rituximab (accessed April 2020)
2. https://www.medicines.org.uk/emc methotrexate (accessed April 2020)
3. https://www.medicines.org.uk/emc procarbazine (accessed April 2020)
4. 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.

5. Aintree Hospital NHS Trust RMP protocol
6. Fritsch, K. et al. High-dose methotrexate-based immune-chemotherapy for elderly primary CNS lymphoma patients (PRIMAIN study). Leukemia 2017;31 846-852

Circulation/Dissemination

Date added into Q-Pulse	For completion by DCM
Date document posted on the Intranet	For completion by DCM

Version History

Date	Version	Author name and designation	Summary of main changes
24/3/2021	1.0		To be completed by author
8/6/2023	2.0	**Jenny Gibson. Haematology Pharmacist**	**Transferred to new template** **Seperated into 14 day cycles to allow transfer to electronic prescribing system** **Addition of maintenance procarbazine** **Remove requirement to stop infusion after 3 hours**
1/11/2023	3.0	**Jennifer Gibson (HO Pharmacist)**	**Updated the calcium folinate dosing adjustment for levels information. Rituximab IRR table added**