Systemic Anti Cancer Therapy Protocol

NORDIC (R-maxi-CHOP alternating with R- HD cytarabine) Mantle Cell Lymphoma

PROTOCOL REF: MPHANORDHA
(Version No. 2.0)

Approved for use in:

- First line treatment of mantle cell lymphoma (stage II to IV) in patients suitable for intensive treatment (including stem cell transplantation)

Blueteq registration not required

Dosage Cycle 1, 3 and 5:

Drug	Dose	Route	Frequency
Prednisolone	**100mg**	PO	Days 1 to 5
Rituximab	**375mg/m^2**	IV infusion	Day 1
Cyclophosphamide	**1200mg/m^2**	IV infusion	Day 1
Doxorubicin	**75mg/m^2**	IV infusion	Day 1
Vincristine	**1.4mg/m^2** (max dose 2mg)	IV infusion	Day 1

Dosage Cycle 2, 4 and 6:

Drug	Dose	Route	Frequency
Rituximab	**375mg/m^2**	IV infusion	Day 1
Cytarabine	**3000mg/m^2** *	IV infusion	Twice a day days 1 and 2

***Consider reducing to 2000mg/m^2 if patients >60 years old or other comorbidities**

Maximum of 6 cycles (21 day cycle)

Administration:

- Due to the long retention time of rituximab in B cell depleted patients, women of childbearing potential must employ effective contraceptive methods during and for 12 months after treatment with rituximab.
- Cycles 2, 4 and 6 require an inpatient stay
- High dose cytarabine can cause conjunctivitis – patients will be given steroid eye drops to prevent this

Anti-emetic risk:

MaxiCHOP: Severely emetogenic.
High dose cytarabine: Severely emetogenic

Supportive treatments:

Rituximab pre-infusion medication:

- Paracetamol tablet orally 1gram
- Chlorphenamine injection IV bolus 10mg
- Cycle 3 and 5 prednisolone should be given at least 30 minutes before the rituximab
- Cycle 2, 4 and 6 hydrocortisone 100mg IV at least 30 minutes before the rituximab

Supportive medication:

- Allopurinol 300mg daily for the first two cycles
- Corticosteroid eye drops 1 drop into both eyes four times a day on days 1-7 for cycles 2,4 and 6 days
- Ondansetron PO 8mg BD for three days (MaxiCHOP) or five days (Cytarabine)
- Metoclopramide PO 10mg three times a day when required
- Docusate PO 100mg twice a day when required
- Co-trimoxazole PO 480mg daily
- Fluconazole 50mg daily
- Filgrastim (Zarzio). Dose is weight dependent. To start on day 5 and administer subcutaneously once daily for 5 days (liaise with transplant team before start of cycle 6 if patient is to be harvested, as patient may need bigger dose and/or longer course)

- MESNA 400mg pre treatment, 400mg two hours post treatment, 400mg six hours post treatment (give with cycles 1,3 and 5)

Extravasation risk:

Rituximab: non-vesicant

Cyclophosphamide: non-vesicant

Doxorubicin: vesicant

Vincristine: vesicant

Cytarabine: non-vesicant

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

Interactions:

Rituximab

No significant interactions

Cyclophosphamide

Substances that reduce the efficacy of cyclophosphamide include:
aprepitant, bupropion, busulfan,ciprofloxacin, chloramphenicol, azole-antimycotics (e.g, fluconazole and itraconazole, CYP2B6 and CYP3A4 inhibitors (e.g. nevirapin and ritonavir): co-administration may reduce the efficacy of cyclophosphamide, prasugrel, sulfonamides, e.g. sulfadiazine, sulfamethoxazoel and sulfapyridine, thiotepa, grapefruit (fruit or juice), rifampicin, St. John’s wort.

An increased risk of side-effects may occur with:
Azathioprine: increased risk of hepatotoxicity (liver necrosis), chloral hydrate, cimetidine, disulfiram, glyceraldehyde, protease inhibitors, saquinavir, rifampin, phenobarbital, carbamazepine, phenytoin, St. John's wort, benzodiazepines, corticosteroids and dabrafenib.

There is an increased risk of cardiotoxicity when cyclophosphamide is co-administered with:
Anthracyclines, mitomycin, cytarabine, pentostatin and radiation therapy.

Doxorubicin

Doxorubicin undergoes metabolism via CYP450 so concomitant use of inhibitors may increase toxicity and inducers may reduce efficacy.

Ciclosporin and cimetidine increase the AUC of doxorubicin; dose adjustments may be required.

Barbiturates may lead to an accelerated plasma clearance of doxorubicin, while the concomitant administration of phenytoin may result in lower plasma phenytoin levels. Doxorubicin is a potent, radio sensitizing agent.

Vincristine

Care needed with drugs that also cause neurotoxicity.
Vincristine may reduce plasma levels of phenytoin therefore dose adjustment of phenytoin based on levels may be required.

Caution should be exercised in patients concurrently taking drugs known to inhibit drug metabolism by hepatic cytochrome P450 isoenzymes in the CYP 3A subfamily, or in patients with hepatic dysfunction.

When chemotherapy is being given in conjunction with radiation therapy through portals which include the liver, the use of vincristine should be delayed until radiation therapy has been completed.

Cytarabine

Cytarabine may reduce digoxin plasma concentrations and therefore monitoring of digoxin levels is recommended.

An *in-vitro* interaction study between gentamicin and cytarabine showed a cytarabine related antagonism for the susceptibility of *K. pneumoniae* strains. In patients on cytarabine being treated with gentamicin for a *K.pneumoniae* infection, a lack of a prompt therapeutic response may indicate the need for re-evaluation of antibacterial therapy.

Intravenous cytarabine given concomitantly with intrathecal methotrexate may increase the risk of severe neurological adverse reactions such as headache, paralysis, coma and stroke like episodes.

Cycle 1, 3 and 5 Treatment Schedule:

Day	Drug	Dose	Route	Diluent and rate
1	**Prednisolone**	**100mg**	**PO**	To be taken at least 30 minutes before rituximab
	Paracetamol	**1000mg**	**PO**	
	Chlorphenamine	**10mg**	**IV**	
	Rituximab	**375mg/m^2**	**IV**	In 500mls Sodium chloride 0.9%. For rate see rituximab rate protocol
	Ondansetron	**8mg**	**IV**	Over 15 minutes
	MESNA	**400mg**	**PO**	
	Vincristine	**1.4mg/m^2** (max dose 2mg)	**IV**	In 50ml Sodium chloride 0.9% over 15 minutes
	Doxorubicin	**75mg/m^2**	**IV**	In 100mls Sodium chloride 0.9% over 30 minutes
	Cyclophosphamide	**1200mg/m^2**	**IV**	In 250mls Sodium chloride 0.9% over 30 minutes
2 to 5	**Prednisolone**	**100mg**	**PO**	

Cycle 2, 4 and 6 Treatment Schedule:

Day	Drug	Dose	Route	Diluent and rate
1 **AM**	**Paracetamol**	**1000mg**	**PO**	
	Chlorphenamine	**10mg**	**IV**	
	Hydrocortisone	**100mg**	**IV**	
	Rituximab	**375mg/m^2**	**IV**	In 500mls Sodium chloride 0.9%. For rate please see rituximab rate protocol.
	Ondansetron	**8mg**	**IV**	Over 15 minutes
	Cytarabine	**3000mg/m^2***	**IV**	In 500mls Sodium chloride 0.9% over 3 hours
1	**Ondansetron**	**8mg**	**IV**	Over 15 minutes

PM	**Cytarabine**	**3000mg/m^2***	**IV**	In 500mls Sodium chloride 0.9% over 3 hours
2 **AM**	**Ondansetron**	**8mg**	**IV**	Over 15 minutes
	Cytarabine	**3000mg/m^2***	**IV**	In 500mls Sodium chloride 0.9% over 3 hours
2 **PM**	**Ondansetron**	**8mg**	**IV**	Over 15 minutes
	Cytarabine	**3000mg/m^2***	**IV**	In 500mls Sodium chloride 0.9% over 3 hours

Consider reducing to 2000mg/m^2 if patients >60 years old or other comorbidities

Main toxicities:

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

Investigations and treatment plan:

	Pre	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6 day 1	Cycle 6 day 9	Ongoing
Informed Consent	X								
Clinical Assessment	X	X	X	X	X	X	X		
SACT Assessment (including toxicity assessment and PS)		X	X	X	X	X	X	X	
Blood pressure	X	X	X	X	X	X	X	X	Continuous monitoring required if on rituximab
Temperature, respiratory rate, pulse		X	X	X	X	X	X	X	Continuous monitoring required if on rituximab
FBC	X	X	X	X	X	X	X	X	
U&E, LFTs and bone profile	X	X	X	X	X	X	X		
CrCl (Cockcroft and gault)	X								
HbA1C	X								Repeat as clinically indicated
CT or PET CT Scan	X								Interim and end of treatment scans as indicated
Bone Marrow	X								Repeat as clinically indicated
ECHO or MUGA Scan	X								Before treatment in patients over 60 or with pre-existing cardiac disease
Hepatitis B core antibody and surface antigens & Hep C & HIV 1+2	X								
Pregnancy test	X								Where appropriate
Height	X								
Weight	X	X	X	X	X	X	X	X	

Dose Modifications and Toxicity Management:

Complete this guidance in line with SPC/ other protocols or trial protocols

Non-haematological toxicity:

Maxi RCHOP:

General	Modification
Existing cardiac comorbidities or excess toxicity from previous cycle	Reduce doxorubicin to 50mg/m2 **AND** Reduce cyclophosphamide to 750mg/m2 (63%)

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

Vincristine		
	Grade	**Modification**
Neurotoxicity	Grade 2 motor weakness or grade 3 sensory toxicity	Give 50% vincristine

	Higher grades of neurological toxicity	Omit vincristine
Elderly Population	Consider reducing the dose to 1mg for patients >70years old.	

Haematological toxicity:

Neutrophils (x10^9/L)	**Modification**
Neutrophils <1.0 on day treatment due	Delay cycle one week and give GCSF with subsequent cycles
Neutrophils <0.5 or febrile neutropenia following any cycle of CHOP	All subsequent cycles give GCSF support
Neutrophils <0.5 leading to infection despite GCSF support	Consider 50% dose reduction of cyclophosphamide and doxorubicin for all subsequent cycles
Neutrophils <0.5 despite 50% dose reduction in cyclophosphamide and doxorubicin	Consider termination of protocol
Platelets (x10^9/L)	**Modification**
Platelets <100 on day treatment due	Delay cycle one week.
Platelets < 50 following any cycle of CHOP	Reduce dose of cyclophosphamide and doxorubicin by 50% for all subsequent cycles
Platelets < 50 despite 50% dose reduction in cyclophosphamide and doxorubicin	Consider termination of protocol
The above haematological toxicities are those relating to maxiCHOP treatment. If patients develop repeated severe grade 3-4 toxicities it is questionable whether they are fit enough to proceed to high dose cytarabine cycles, unless this relates to marrow infiltration in early cycles. **High dose cytarabine should not commence unless Neutrophil count >1 x10^9/L and platelets >100 x10^9/L**	

Dosing in renal and hepatic impairment:

Cyclophosphamide	
Renal Function	
CrCl (ml/min)	Dose
10-29	Consider 75% of dose
<10 or haemodialysis	Not recommended. If unavoidable consider 50% of dose.
Liver Function	
Severe liver dysfunction	Not recommended

Vincristine

Liver Function	
Bilirubin (micromole/L)	Dose
<51	50% of dose

Doxorubicin	
Renal Function	
Haemodialysis	Consider 75% of dose
Liver Function	
Bilirubin (micromole/L)	Dose
20-50	50%
51-86	25%
>86 or Child Pugh C	Omit

Cytarabine	
Renal Function	
CrCl (ml/min)	Dose
31-59	50%
<30	Not recommended
Liver Function	Dose
Severe dysfunction	Consider 25-50% of dose and increase if tolerated.

References:

1. https://www.medicines.org.uk/emc rituximab (accessed May 2020)
2. https://www.medicines.org.uk/emc cyclophosphamide (accessed May 2020)
3. https://www.medicines.org.uk/emc vincristine (accessed May 2020)
4. https://www.medicines.org.uk/emc doxorubicin (accessed May 2020)
5. https://www.medicines.org.uk/emc cytarabine (accessed May 2020)
6. 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.
7. MaxiRCHOP/ High dose ARA-C protocol. Thames valley Strategic Clinical Network, May 2019

http://nssg.oxford-haematology.org.uk/lymphoma/documents/lymphoma-chemo-protocols/L-84-maxi-chop-arac-r.pdf

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
Aug 2023	2	**Aileen McCaughey HO Pharmacist**	Updated to new version of SACT protocol. PO ondansetron switched to IV ondansetron prior to maxi-CHOP and cycle 6 day 9 rituximab removed (cycle 1 now includes rituximab)