Nordic Protocol (Maxi-CHOP and High Dose Cytarabine) for Mantle Cell Lymphoma (MCL)

Indication: Mantle Cell Lymphoma, Stage II to IV, < 60-65 years, good performance status.

Rituximab for this protocol is funded via the CDF.

Regimen details:

Cycle 1: Maxi-CHOP 21 (No Rituximab in cycle 1)

Cyclophosphamide	1200mg/m^2		IV	Day 1
Doxorubicin	75mg/m^2		IV	Day 1
Vincristine	2mg		IV	Day 1
Prednisolone	100mg		Orally	Days 1 to 5

Cycles 2 and 4: R-High Dose Cytarabine

Rituximab	375mg/m^2		IV	Day 1
Cytarabine	3000mg/m^2	BD	IV	Days 1 and 2

Cycles 3 and 5: R-Maxi-CHOP 21

Rituximab	375mg/m^2		IV	Day 1
Cyclophosphamide	1200mg/m^2		IV	Day 1
Doxorubicin	75mg/m^2		IV	Day 1
Vincristine	2mg		IV	Day 1
Prednisolone	100mg		Orally	Days 1 to 5

Cycle 6: R-High Dose Cytarabine + R Stem Cell Mobilisation

Rituximab	375mg/m^2		IV	Days 1 and 9
Cytarabine	3000mg/m^2	BD	IV	Days 1 and 2

GCSF as per Stem Cell Transplant Team for this cycle.

Administration:

Rituximab	IV infusion in 500ml sodium chloride 0.9%. Rate as per rituximab administration guidance.
Cyclophosphamide	IV infusion in 100 - 250ml sodium chloride 0.9% over 30 minutes or as an IV bolus
Doxorubicin	Slow IV bolus into the side arm of a free-running drip of sodium chloride 0.9%
Vincristine	IV infusion in 50ml sodium chloride 0.9% over 5 minutes.
Prednisolone	Orally, with or after food. Available as 5mg and 25mg tablets.
Cytarabine	IV infusion in 1000ml sodium chloride 0.9% over 3 hours.

Premedication: 30 minutes prior to rituximab:

Paracetamol	1000mg	orally
Chlorphenamine	10mg	IV
Prednisolone	100mg	orally (Day 1 of Maxi-CHOP chemotherapy) OR
Hydrocortisone	100mg	IV

Frequency: Every 21 days (3 cycles of each regimen, alternating)

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Extravasation: Vincristine and doxorubicin are vesicants and should be administered with appropriate precautions to prevent extravasation.
If there is any possibility that extravasation has occurred, contact a senior member of the medical team and follow local protocol for dealing with cytotoxic extravasation
Cyclophosphamide, cytarabine and rituximab are not vesicants.

Anti- emetics: High emetogenic potential (60% - 90%) incidence. Follow local anti-emetic policy.

Supportive medication: Allopurinol 300mg od orally (100mg if renal impairment) for prevention of tumour lysis syndrome for first cycle only.
PPI prophylaxis e.g. omeprazole 20mg od orally.
For Maxi-CHOP cycles: Mesna 800mg 2 hours pre-CHOP and 2 and 6 hours post-CHOP.
For High Dose Cytarabine cycles: Corticosteroid eye drops as per local formulary (e.g. prednisolone (Predsol®) 0.5% or dexamethasone (Maxidex®) 0.1%), during and for 3 days after completion of chemotherapy
GCSF: preparation as per local policy. For primary prophylaxis of febrile neutropenia as per local policy.

Regular investigations:

Baseline & regular	
FBC	Prior to each cycle
LFTs	Prior to each cycle
U&Es	Prior to each cycle

Dose Modifications

Haematological Toxicity

Cycle 1 will go ahead full dose even if FBC is not normal.

Neutrophils (x 10^9/L)		Platelets (x 10^9/L)	CHOP
≥1.5 x 10^9/L	&	≥ 100 x 10^9/L	100% dose
<1.5 x 10^9/L	or	< 100 x 10^9/L	Delay until neutrophils > 1.5 x 10^9/L and platelets > 100 x 10^9/L

Renal Impairment

CrCl (ml/min)	Cyclophosphamide Dose
> 20	Give 100%
10 – 20	Give 75%
< 10	Give 50%

High dose cytarabine: consider dose reduction if CrCl < 60ml/min
Doxorubincin and vincristine: no dose reductions required.

Confirm any dose reductions with the Consultant, because in some circumstances 100% dose may be appropriate.

Reason for Update: Network Protocol Development	Approved by Consultant: Paul Fields
Version: 1	Approved by Chair Haem TWG: Majid Kazmi
Supersedes: All other versions	Date: 02 Oct 2012
Prepared by: Laura Cameron	Checked by (Network Pharmacist): Jacky Turner 19 Sept 2012

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Hepatic Impairment

Bilirubin (µmol/l)	Doxorubicin Dose
20 – 50	50%
51 – 85	25%
> 85	Omit
Bilirubin (µmol/l)	Vincristine Dose
< 51	100%
> 51 - 85	50%
> 85	Omit
Bilirubin (µmol/l)	Cytarabine Dose
< 34	100% dose
> 34	50% dose

Confirm any dose reductions with the Consultant, because in some circumstances 100% dose may be appropriate.

Toxicities: Myelosuppression, cardiotoxicity
Neurotoxicity – monitor for constipation or peripheral sensory loss and discuss with Consultant before administering further cycles. Consider dose reducing vincristine to 1mg or substituting for vinblastine.
Cytarabine: ocular pain, foreign body sensation, photophobia and blurred vision.
Dizziness, headache, confusion, cerebellar toxicity. Skin freckling, itching, at injection site, rash, skin sloughing of the palmar and plantar surfaces. Myalgia and bone pain

Drug interactions: Concurrent administration of vincristine and itraconazole, voriconazole, posaconazole have been reported to cause increased severity of neuromuscular side effects and are therefore contra-indicated.

Comments: Maximum cumulative lifetime dose doxorubicin = 450 - 550mg/m^2
A baseline MUGA scan should be performed where the patient is considered at risk of having impaired cardiac function e.g. significant cardiac history, hypertension, obese, smoker, elderly, previous exposure to anthracyclines, previous thoracic radiotherapy. MUGA scan should be repeated if there is suspicion of cardiac toxicity at any point during treatment, or if cumulative anthracycline dose approaches maximum.

References: Geisler C.H. *et al.* Long-term progression-free survival of mantle cell lymphoma after intensive front-line immunochemotherapy with in vivo-purged stem cell rescue: a nonrandomised phase 2 multicenter study by the Nordic Lymphoma Group. Blood 2008; 112: 2687-2693