

DERBY-BURTON LOCAL CANCER NETWORK			
FILENAME	NORDIC.DOC	CONTROLLED DOC NO:	HCCPG B123
CSIS Regimen Name:	NORDIC_1 = Cycle 1	NORDIC_5 = Cycle 5	
	NORDIC_2 = Cycle 2	NORDIC_6 = Cycle 6	
	NORDIC_3 = Cycle 3	<i>See notes below for further details</i>	
	NORDIC_4 = Cycle 4		

Nordic Protocol (MaxiCHOP/R-MaxiCHOP plus R-HDAraC)

Available for Routine Use in			
Burton in-patient		Derby in-patient	✓ (First cycle if bulky disease & risk of tumour lysis syndrome)
Burton day-case	✓	Derby day-case	✓
Burton community		Derby community	
Burton out-patient		Derby out-patient	

Indication	Mantle cell lymphoma for patients <70 yrs suitable for intensification with autologous stem cell transplant		
Treatment Intent	Radical		
Anti-Emetics	Pre-chemotherapy	3 – Maxi-CHOP	
		2 – High dose cytarabine	
	Post-chemotherapy	A	
Frequency & Duration	See below		

Cycle 1: MaxiCHOP

Day 1	Ondansetron	8mg	As a single oral or intravenous dose prior to chemotherapy
	Prednisolone	100mg	Oral once daily for 5 days
	Mesna	240mg/m ²	Intravenous infusion in 100ml 0.9% sodium chloride over 15-30 minutes, prior to cyclophosphamide
	Cyclophosphamide	1200mg/m ²	Intravenous bolus
	Doxorubicin	75mg/m ²	Intravenous bolus
	Vincristine	1.4mg/m ²	Intravenous infusion in 50ml sodium chloride 0.9% over 5-10 minutes
		maximum 2mg (See notes)	
	Mesna	480mg/m ²	Oral, 2 hours and 6 hours after cyclophosphamide (<i>2 doses in total</i>)
	Omeprazole	20mg	Oral once daily for 5 days
	Allopurinol	300mg	Oral once daily for 1-2 cycles
	Metoclopramide	10mg	Oral four times daily as required

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Cotrimoxazole	480mg	Oral once daily for 21 days
Aciclovir	400mg	Oral twice daily for 21 days

Cycle 2 and 4: High-dose cytarabine + Rituximab

Day 1	Paracetamol	1g	As a single oral dose 30 minutes prior to rituximab
	Chlorphenamine	4mg PO or 10 mg IV	As a single dose 30 minutes prior to rituximab
	Hydrocortisone	100mg	As a single intravenous bolus 30 minutes prior to rituximab
	Rituximab	375mg/m ²	Intravenous infusion in 500ml sodium chloride 0.9%
	Ondansetron	8mg	As a single oral or intravenous dose prior to each dose of cytarabine
	Dexamethasone	8mg	As a single oral or intravenous dose prior to each dose of cytarabine
	Cytarabine*	3000 mg/m ²	Intravenous infusion in 1000ml sodium chloride 0.9% over 3 hours every 12 hours for 2 doses
	Prednisolone (Predsol 0.5%)	1 drop	Eye drops 4 times daily in each eye for 7 days
	Allopurinol	300mg	Oral once daily for 1-2 cycles
	Metoclopramide	10mg	Oral four times daily as required
	Cotrimoxazole	480mg	Oral once daily for 21 days
	Aciclovir	400mg	Oral twice daily for 21 days
	Itraconazole	200mg	Oral twice daily for 14 days only (See notes below)
Day 2	Ondansetron	8mg	As a single oral or intravenous dose prior to each dose of cytarabine
	Dexamethasone	8mg	As a single oral or intravenous dose prior to each dose of cytarabine
	Cytarabine*	3000 mg/m ²	Intravenous infusion in 1000ml sodium chloride 0.9% over 3 hours every 12 hours for 2 doses
	Metoclopramide	10mg	Oral four times daily as required
Day 7	GCSF	300 micrograms	Subcutaneous injection once daily until neutrophils >1.0x10 ⁹ /l

- see dose modifications below for patients aged >60.

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Cycle 3 and 5: MaxiCHOP + Rituximab

Day 1	Ondansetron	8mg	As a single oral or intravenous dose prior to chemotherapy
	Paracetamol	1g	As a single oral dose 30 minutes prior to rituximab
	Chlorphenamine	4mg PO or 10 mg IV	As a single dose 30 minutes prior to rituximab
	Hydrocortisone	100mg	As a single intravenous bolus 30 minutes prior to rituximab
	Prednisolone	100mg	Oral once daily for 5 days- Day 1 to be given 30 minutes prior to rituximab
	Rituximab	375mg/m ²	Intravenous infusion in 500ml sodium chloride 0.9%
	Mesna	240mg/m ²	Intravenous infusion in 100ml 0.9% sodium chloride over 15-30 minutes, prior to cyclophosphamide
	Cyclophosphamide	1200mg/m ²	Intravenous bolus
	Doxorubicin	75mg/m ²	Intravenous bolus
	Vincristine	1.4mg/m ² maximum 2mg (See notes)	Intravenous infusion in 50ml sodium chloride 0.9% over 5-10 minutes
	Mesna	480mg/m ²	Oral, 2 hours and 6 hours after cyclophosphamide (<i>2 doses in total</i>)
	Omeprazole	20mg	Oral once daily for 5 days
	Metoclopramide	10mg	Oral four times daily as required
	Cotrimoxazole	480mg	Oral once daily for 21 days
	Aciclovir	400mg	Oral twice daily for 21 days

Cycle 6: High-dose cytarabine + Rituximab (mobilising cycle)

Day 1	Paracetamol	1g	As a single oral dose 30 minutes prior to rituximab
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	Chlorphenamine	4 mg PO or 10mg IV	As a single dose 30 minutes prior to rituximab
	Hydrocortisone	100mg	As a single intravenous bolus 30 minutes prior to rituximab
	Rituximab	375mg/m ²	Intravenous infusion in 500ml sodium chloride 0.9%
	Ondansetron	8mg	As a single oral or intravenous dose prior to each dose of cytarabine
	Dexamethasone	8mg	As a single oral or intravenous dose prior to each dose of cytarabine
	Cytarabine*	3000mg/m ²	Intravenous infusion in 1000ml sodium chloride 0.9% over 3 hours every 12 hours for 2 doses
	Prednisolone (Predsol 0.5%)	1 drop	Eye drops 4 times daily in each eye for 7 days
	Metoclopramide	10mg	Oral four times daily as required
	Cotrimoxazole	480mg	Oral once daily for 21 days
	Aciclovir	400mg	Oral twice daily for 21 days
	Itraconazole	200mg	Oral twice daily for 14 days only
Day 2	Ondansetron	8mg	As a single oral or intravenous dose prior to each dose of cytarabine
	Dexamethasone	8mg	As a single oral or intravenous dose prior to each dose of cytarabine
	Cytarabine*	3000mg/m ²	Intravenous infusion in 1000ml sodium chloride 0.9% over 3 hours every 12 hours for 2 doses
	Metoclopramide	10mg	Oral four times daily as required
Day 5	GCSF (Lenograstim)	263 micrograms	Subcutaneous injection once daily at 6pm until stem cell collection
Day 9	Paracetamol	1g	As a single oral dose 30 minutes prior to rituximab
	Chlorphenamine	4mg PO or 10 mg IV	As a single dose 30 minutes prior to rituximab
	Hydrocortisone	100mg	As a single intravenous bolus 30 minutes prior to rituximab
	Rituximab	375mg/m ²	Intravenous infusion in 500ml sodium chloride 0.9%

Peripheral blood stem cell mobilization days 14, 15, 16

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	NORDIC_3 = Cycle 3	<i>See notes below for further details</i>	
	NORDIC_4 = Cycle 4		

* see dose modifications below for patients aged >60.

Frequency & duration

6 cycles are given in total with alternating R-maxiCHOP (no Rituximab on cycle1) and R-high dose cytarabine every 21 days. This should be consolidated with a BEAM PBSCT. Stem cells can be mobilised off the back of cycle 6 of R-high dose cytarabine.

Cycle 1 : MaxiCHOP

Cycle 2 ; R + High dose cytarabine

Cycle 3 : R+ MaxiCHOP

Cycle 4 : R + High dose cytarabine

Cycle 5 : R + MaxiCHOP

Cycle 6 : R+ High dose cytarabine plus additional Rituximab Day 9

(mobilizing cycle, must commence on a Monday, GCSF starts day 5, mobilising from day 14).

Notes:

Baseline investigations

Cardiac assessment (e.g. MUGA) in those patients \geq 65 years or those with a cardiac history.

Rituximab

This section should be read in conjunction with the 'Guidelines for the administration of rtuximab'.

1. Premedication consisting of analgesia and an antihistamine and an intravenous corticosteroid should always be administered 30 minutes before each infusion of rituximab (e.g. paracetamol 1g oral STAT and chlorphenamine 4mg oral or 10mg IV bolus STAT and hydrocortisone 100mg IV STAT).
2. Rituximab doses should be rounded to the nearest 100mg.
Use rituximab rate calculator to assist with rate escalation of rituximab infusion.
3. Occurrence of an Infusion Related Event or Hypersensitivity:
Stop the infusion and contact a doctor.
When symptoms improve, continue the infusion at half the rate prior to the reaction.
Accelerate the infusion rate more slowly as tolerated by the patient.

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Dose modifications and toxicities

Patients older than 60 : *consider reducing cytarabine dose to 2g/m² twice daily.*

1. Haematological toxicity

At the start of the each cycle of chemotherapy the neutrophil count should be > 1.0 x 10⁹/l and platelets > 100 x 10⁹/l.

a) Neutropenia

Neutrophils <1.0 x 10 ⁹ /l on day treatment due	Delay one week and give GCSF with subsequent cycles (<i>days 7,9,11 initially</i>)
Grade 4 neutropenia* or febrile neutropenia following any cycle of (R)CHOP	Give GCSF support with all subsequent cycles
Grade 4 neutropenia* leading to infection despite GCSF support	Consider 50% reduction of cyclophosphamide and doxorubicin for all subsequent cycles
Grade 4 neutropenia* recurs despite 50% dose reduction in cyclophosphamide and doxorubicin	Consider termination of protocol

b)Thrombocytopenia

Platelets < 100 on day treatment due	Delay one week
Grade 3 or 4 thrombocytopenia* following any cycle of (R)CHOP	Reduce dose of cyclophosphamide and doxorubicin by 50% for all subsequent cycles
Grade 4 thrombocytopenia* recurs despite 50% dose reduction in cyclophosphamide and doxorubicin	Consider termination of protocol

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2. Renal impairment

Cyclophosphamide

GFR ml/min	Dose
>20	100%
10-20	75%
<10	50%

Cytarabine

GFR ml/min	Dose
>60	100%
46-60	60%
31-45	50%
<30	contraindicated

Dose reduction for renal impairment is not required for doxorubicin or vincristine.

3. Hepatic impairment

Doxorubicin

Bilirubin micromol/L	Dose	AST Units/L	Dose
<20	100%	2-3x ULN	75%
20-51	50%	>3x ULN	50%
52-85	25%		
>85	contraindicated		

Cytarabine

If bilirubin >34 micromol/L give 50% dose

Vincristine

Bilirubin micromol/L	AST/ALT Units/L	Dose
26-51 or	60-180	50%
>51 &	normal	50%
>51 &	>180	omit

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4. Neurotoxicity

Vincristine

If grade 2 motor weakness* or grade 3 sensory toxicity*, reduce dose to 1mg. For higher grade toxicity omit.

Cytarabine

Cerebral and cerebellar toxicity can cause significant and varied neurological manifestations but usually reversible.

5. Other toxicities

Cytosine syndrome is characterised by fever, myalgia, bone pain, occasional chest pains, maculopapular rash, conjunctivitis and malaise. This usually occurs 6-12 hours following infusion, and is more common with higher doses. Systemic steroids have been beneficial in treating this condition if severe.

Supportive care

1. Allopurinol 300mg once daily (Reduce dose to 100mg if GFR < 10ml/min).
2. Co-trimoxazole 480mg ONCE daily. In cases of allergy to co-trimoxazole, consider dapsone 100mg daily.
3. Aciclovir 400mg twice daily.
4. Itraconazole 200mg twice daily during cycles of high dose cytarabine only. It should be given for 14 days at a time **only** as it interacts with vincristine and so should **not** be used during cycles of RCHOP
5. Omeprazole 20mg once daily for 5 days (i.e. concurrently with Prednisolone)
6. GCSF 300 micrograms once daily by sub-cutaneous injection on days 7, 9,11 (& 13) post Maxi-CHOP if ≥ 65 years **or** has developed neutropenic sepsis with previous cycles of chemotherapy. GCSF 300 micrograms once daily from day 7 of high-dose Cytarabine cycles until $ANC > 1.0 \times 10^9/l$.
7. Prednisolone (0.5% Predsol) eye drops (or equivalent) should be used four times a day during the courses of high dose cytarabine and be continued for 5 days after each course finishes.

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***WHO toxicity table**

Toxicity	Grade			
	1	2	3	4
Neutrophils x10 ⁹ /l	1.5-1.99	1.0-1.49	0.5-0.99	<0.5
Platelets x10 ⁹ /l	75-149	50-74	10-49	<10
Neuropathy (motor)	Subjective weakness but no objective findings	Mild objective weakness interfering with function, but not interfering with activities of daily living	Objective weakness interfering with activities of daily living	Paralysis
Neuropathy (sensory)	Loss of deep tendon reflexes or parasthesia (including tingling) but not interfering with function	Objective sensory loss or parasthesia (including tingling) interfering with function, but not interfering with activities of daily living	Sensory loss or parasthesia interfering with activities of daily living	Permanent sensory loss that interferes with function

References

1. Geisler, C.H. *et al* (2008) **Long-term progression-free survival of mantle cell lymphoma after intensive front-line immunochemotherapy with in-vivo purged stem cell rescue: a nonrandomized phase 2 multicenter study by the Nordic Lymphoma Group**, Blood, Vol 112 (7), pp 2687-2693.
2. Burns, S., Collins, D. & Simmons, W. (2010) **Approved Haematology Chemotherapy Protocol Nordic Mantle Cell**, Merseyside and Cheshire Cancer Network
3. Hatton, C. (2011) **MaxiCHOP/High Dose Ara-C + Rituximab, Nordic Protocol version 1.2**, Downloaded September 19th 2012 <
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