NORDIC REGIMEN

INDICATION: Induction treatment of mantle cell lymphoma where autologous stem cell transplant planned

Treatment plan:
Cycle 1 – maxiCHOP, no rituximab
Cycle 2 – rituximab + HD cytarabine
Cycle 3 – rituximab + maxi CHOP
Cycle 4 - rituximab + HD cytarabine
Cycle 5 - rituximab + maxi CHOP
Cycle 6 - rituximab + HD cytarabine + additional rituximab on day 9

Prior to a course of treatment:

- Assess cardiac function by history & exam, ECG and CXR. If there is evidence of cardiac disease or risk factors, prior anthracyclines or patient > 70yrs perform a MUGA scan. If LVEF< 50% *discuss with consultant*
- Check hepatitis B & C serology
- Check FBC. Patient must have adequate marrow reserve - neutrophils >1.0, platelets >75 unless cytopaenia is due to disease, e.g marrow infiltration, splenomegaly
- Check renal and liver function – if bilirubin > 1.5x ULN (unless due to lymphoma) or creatinine clearance < 40ml/min reconsider fitness for this regimen – *discuss with consultant*
- If appropriate discuss possibility of pregnancy with female patients and need for contraception with both male and female patients. Discuss risk of infertility - offer semen cryopreservation to male patients
- If PBSC harvest planned inform transfusion lab that further blood products must be irradiated beginning from 7 days prior to harvest until completion.
- Assess venous access or arrange for insertion of femoral line following cycle 6 with a view to apheresis
- Written consent for course

Prior to each cycle:

- Medical review of fitness for chemotherapy – exclude active infection, major changes in organ function
- Check FBC - neutrophils should be >1.0 and platelets >75**.** If these parameters are not reached despite 2 week delay reconsider suitability for this regimen.
- Check renal and liver function – if bilirubin > 1.5x ULN or creatinine clearance < 40ml/min reconsider suitability for this regimen – *discuss with consultant*

Maxi-(R)-CHOP cycles 1, 3, 5

Rituximab	375mg/m^2	IV in 0.5L N saline	day 1 **(cycles 3 & 5 only)**
Cyclophosphamide	1200mg/m^2	IV bolus or infusion	day 1
Doxorubicin	75mg/m^2	IV bolus	day 1
Vincristine	2mg	IV bolus	day 1
Prednisolone	100mg	PO	days 1-5

R-HDAC cycles 2, 4, 6

Rituximab	375mg/m^2	IV in 0.5L N saline	day 1 (**also day 9 with cycle 6**)
Cytarabine	3g/m^2 12 hrly (2g/m^2 if over 60yrs)	IV in 1.oL Nsaline	day 1 & 2 (4 doses)
GCSF (**cycle 6 only**)	10mcg'kg od	sc	from day 10 until PBSC harvesting completed

Cycles to be repeated every 21 days

Prophylaxis for acute emesis	5HT antagonist
Prophylaxis for delayed emesis	5HT antagonist + metoclopramide 3-4 days
Other medications	Allopurinol 300mg od days 1-5 for cycle 1
	Prednisolone 0.5% eye drops each eye tds days 2-8 (cycles 2,4,6)
	Anti-infective prophylaxis according to local policy

For cardiotoxicity

- If symptoms or signs of cardiac failure develop, discontinue doxorubicin and measure LVEF by MUGA scan. *Inform consultant*.

For vincristine neurological toxicity

• Grade 2 motor (*mild <u>objective</u> weakness interfering with function but not with activities of daily living*) or grade 3 sensory (*sensory loss or paresthesia interfering with activities of daily living*) toxicity	Reduce vincristine dose to 1mg
• Neurological toxicity increases despite reduction.	Stop vincristine

For haematological toxicity

• No dose modification for cycle 1	
• Consider primary GCSF prophylaxis	
• Neutrophils < 1.5 on day treatment due	Delay 1 week and give GCSF for subsequent cycles
• Neutropenic sepsis or grade 4 neutropenia with any cycle	Give GCSF with subsequent cycles
• Grade 4 neutropenia, neutropenic sepsis despite GCF	Consider 50% dose reduction cyclophosphamide, doxorubicin with subsequent cycles
• Recurrent grade 4 neutropenia, neutropenic sepsis despite dose reduction	Reconsider patient suitability for further treatment – *discuss with consultant*

For renal impairment

- Creatinine clearance > 20ml/min — 100% dose cyclophosphamide
- Creatinine clearance 10-20ml/min — 75% dose cyclophosphamide
- Creatinine clearance <10ml/min — 50% dose cyclophosphamide

Consider dose reduction for cytarabine if <60ml/min

For hepatic impairment

Bilirubin umol/l		AST	
21 – 50	50% doxorubicin	2-3 x ULN	75% doxorubicin
51 – 85	25% doxorubicin	More than 3 xx ULN	50% dorubicin
>85	Omit		

If bilirubin > 51umol/l use 50% vincristine. Consider reduced dose cytarabine if there is significant liver dysfunction

R-CHOP21/HDAC toxicities

Neutropenic sepsis	Mucositis
Thrombocytopenia	Sensory & motor neuropathy
Nausea & vomiting (moderate)	Autonomic neuropathy (constipation, ileus)
Alopecia	Amenorrhoea & infertility (offer semen cryopreservation)
Cardiomyopathy	Jaw pain
Hyperglycaemia	Haemorrhagic cystitis
Fever, hypotension, rigors, anaphylaxis (rituximab)	Conjunctivitis
Cerebellar toxicity	'Cytarabine syndrome' - fever, myalgia, bone pain, maculopapular rash (often palmar-plantar)

Reference

Long tem progression free survival of mantle cell lymphoma after intensive front-line chemoimmunotherapy with in vivo purged stem cell rescue: a non-randomised phase 2 multicentre study by the Nordic lymphoma group. Geisler CH et al. Blood 2008; 112(7); 2687-2693

Written by Dr MP Macheta, Consultant Haematologist

Date July 2013

Review July 2015