NORDIC

Indication

Mantle cell lymphoma (for patients suitable for subsequent chemotherapy with haematopoietic stem cell rescue)

ICD-10 code

C83.13

Regimen details

(R) maxi-CHOP – cycles 1, 3 and 5

Days	Drug	Dose	Route
1-5	Prednisolone	100mg	PO
1	Rituximab	375mg/m^2	IV infusion
1	Cyclophosphamide + Mesna (see below)	1200mg/m^2	IV bolus or infusion
1	Doxorubicin	75mg/m^2	IV bolus
1	Vincristine	1.4mg/m^2 (maximum dose 2mg)	IV infusion

(R) high dose cytarabine – cycles 2 and 4

Days	Drug	Dose	Route
1	Rituximab	375mg/m^2	IV infusion
1 and 2	Cytarabine	3g/m^2 every 12 hours (total 4 doses) (2g/m^2 for patients > 60years of age)	IV infusion

Prednisolone 0.5% eye drops QDS for 5-7 days.

(R) high dose cytarabine with haematopoietic stem cell harvest – cycle 6

Days	Drug	Dose	Route
1 and 9	Rituximab	375mg/m^2	IV infusion
1 and 2	Cytarabine	3g/m^2 every 12 hours (total 4 doses) (2g/m^2 for patients >60yr of age)	IV infusion
5 to end of harvest	G-CSF	As per local policy	SC

Prednisolone 0.5% eye drops QDS for 5-7 days.

Haematopoietic stem cell collection should be scheduled for days 14, 15 and 16 of cycle 6.

1-2 weeks after a successful stem cell harvest, it is expected that patients will undergo high dose BEAM or BEAC chemotherapy with haematopoietic stem cell rescue.

Cycle frequency

21 days

Number of cycles

As above, total of 6 cycles (3 x maxi-CHOP and 3 x high dose cytarabine)

After 4 cycles of treatment restage with CT scan of neck, chest, abdomen and pelvis (with IV and oral contrast):

- If progressive disease, give alternative treatment.
- If partial remission, continue with 2 further courses and restage.
- If good, partial or complete response after 6 cycles and successful stem cell harvest, proceed to high dose BEAM/BEAC chemotherapy with stem cell rescue.

Administration

Patients with bulky disease should receive pre-hydration with 2-3L sodium chloride 0.9% over 6-18 hours.

(R) maxi-CHOP

Rituximab is administered in 500mL sodium chloride 0.9%. The first infusion should be initiated at 50mg/hour and if tolerated the rate can be increased at 50mg/hour every 30 minutes to a maximum of 400mg/hour. Subsequent infusions should be initiated at 100 mg/hour and if tolerated increased at 100mg/hour increments every 30 minutes to a maximum of 400 mg/hour.

Cyclophosphamide is administered by slow IV bolus. Mesna is also required due to the high dose of cyclophosphamide. This may be given orally or IV:
Oral mesna at a dose of 40% of the intravenous cyclophosphamide dose for a total of 3 doses, 4 hourly beginning 2 hours before the cyclophosphamide (a total dose of mesna equivalent to 120% of the cyclophosphamide). In patients at high-risk of urothelial toxicity, a shorter interval may be left between oral mesna doses, or the number of doses increased, or both. Discuss with the consultant.
or
IV mesna at a dose of 20% of the dose of cyclophosphamide at the same time as the cyclophosphamide, followed by two oral doses (each 40% of the dose of the cyclophosphamide) given 2 and 6 hours after the intravenous dose.

Doxorubicin is administered by slow IV bolus into the arm of a fast running drip of sodium chloride 0.9%.

Vincristine is administered in 50mL sodium chloride 0.9% over 10 minutes, as per national guidance. Nurse to remain with patient throughout infusion.

(R) high dose cytarabine

Rituximab is administered as above.

Cytarabine is administered in 1000mL sodium chloride 0.9% over 3 hours every 12 hours on days 1 and 2. A total of 4 doses are given.

Pre-medication

Antiemetics as per local policy.
Rituximab premedication:

- Paracetamol 1g PO 60 minutes prior to rituximab infusion
- Chlorphenamine 10mg IV bolus 15 minutes prior to rituximab infusion
- Dexamethasone 8mg IV bolus or Hydrocortisone 100mg IV bolus 15 minutes prior to rituximab infusion (may be omitted if day 1 prednisolone 100mg PO has been taken at least 30 minutes prior to the start of the rituximab infusion)

Emetogenicity

Both regimens have high emetic potential.

Additional supportive medication

Allopurinol 300mg OD during cycle 1 (100mg if creatinine clearance <20mL/min)
Mouthwashes as per local policy
H_2 antagonist or PPI as per local policy
Antibacterial prophylaxis as per local policy
Prednisolone 0.5% eye drops QDS (to avoid chemical conjunctivitis from high-dose cytarabine)
Mesna as above or as per local policy

Extravasation

Doxorubicin and vincristine are vesicant (Group 5)
Rituximab, cytarabine and cyclophosphamide are neutral (Group 1)

Investigations – pre first cycle

Investigation	**Validity period** (or as per local policy)
FBC (with film)	72 hours
U+E (including creatinine)	72 hours
LFTs	72 hours
Glucose	72 hours
Calcium	72 hours
Magnesium	72 hours
Igs, β_2 microglobulin	72 hours

Hepatitis B and C serology should be carried out in addition to EBV, CMV, VZV, HIV 1+2 tests.
Urine pregnancy test in women aged 12 - 55 years of age unless they have been sterilised or undergone a hysterectomy.
ECG +/- echocardiogram - if clinically indicated.

Investigations – pre subsequent cycles

Investigation	**Validity period** (or as per local policy)
FBC	Every 7 days for first 2 cycles* (to identify if blood product support required)
U+E (including creatinine)	Every 7 days for first 2 cycles
LFTs	Every 7 days for first 2 cycles

* The frequency of monitoring can be reduced to 3 weekly (or within 96 hours of next cycle) if very stable

Standard limits for administration to go ahead

Investigation	**Limit**
Neutrophils*	$\geq 1.0 \times 10^9$/L
Platelets*	$\geq 75 \times 10^9$/L
CrCl	≥ 40mL/min
Bilirubin	< ULN
AST/ALT	< 2 x ULN

* if not within range this may be due to marrow and/or splenic involvement by lymphoma and may still be an indication to treat. Discuss with consultant.

Dose modifications

- **Haematological toxicity**

Treatment decisions relating to haematological toxicity should be discussed with the consultant as above.
Neutrophils:

Neutrophils (x 10^9/L)	**Action**
≥ 1.0	100% doses
>0.5-1.0	If patient well: 100% dose + GCSF as per local policy If patient not well: delay 1 week (or until recovery)
≤ 0.5	Delay 1 week

Platelets:

Platelets (x 10^9/L)	**Action (R) maxi CHOP**	**Action (R) high dose cytarabine**
≥ 75	100% doses	100% doses
50-74	75% dose cyclophosphamide 75% dose doxorubicin	Delay 1 week (or until recovery)
< 50	Delay 1 week (or until recovery)	Delay 1 week (or until recovery)

G-CSF support may be required as per local policy

- **Renal impairment**

Doxorubicin is mainly metabolised by the liver. Consultant decision in severe renal impairment.
Vincristine: no dose adjustment required.

CrCl (mL/min)	**Cyclophosphamide dose**	**Cytarabine dose**
> 60	100%	100%
46-60		60%
31-45		50%
21-30		Discontinue
10-20	75%	
<10	50%	

As the intention is to proceed to high dose BEAM/BEAC chemotherapy and stem cell rescue, consultant decision as to whether this regimen is suitable for patients with severe renal impairment.

- **Hepatic impairment**

Bilirubin (x ULN)		**AST/ALT** (x ULN)	**Doxorubicin dose**
< 1	and	< 2	100%
< 1	and	2-3	75%
1-2.5	or	> 3	50%
2.5- 4			25%
> 4			Omit

Bilirubin (x ULN)		**AST/ALT** (x ULN)	**Vincristine dose**
< ULN	and	≤ 2	100%
1 – 2.5	or	> 3	50%
> 2.5	and	< ULN	50%
> 2.5	and	> 3	Omit

Cytarabine dose should be reduced to 50% if bilirubin > 1.5 x ULN. Doses may be escalated in subsequent cycles in the absence of toxicity (consultant decision).

- **Other toxicities**

If previous or existing cardiac history, consider doxorubicin dose reduction. Consultant decision.

Toxicity	**Definition**	**Dose adjustment**
Cardiotoxicity	Ejection fraction by transthoracic echocardiography <40	Omit doxorubicin or consider switching to R-high dose cytarabine only
Neurotoxicity	Grade 2	Reduce vincristine to 50% dose
	Grade 3-4	Omit Vincristine

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects:**

Myelosuppression
Neutropenic sepsis
Infertility/Early menopause
Tumour lysis syndrome
Cardiotoxicity
Neurotoxicity
Hepatic dysfunction
Acute pulmonary toxicity
Cytarabine syndrome (characterised by fever, myalgia, bone pain, occasional chest pains, maculopapular rash, conjunctivitis and malaise. It usually occurs 6 to 12 hours following administration)

- **Frequently occurring side effects:**

Diarrhoea, constipation
Fatigue
Nausea and vomiting
Myelosuppression
Alopecia
Mucositis
Peripheral neuropathy
Conjunctivitis (cytarabine)

- **Other side effects:**

Haemorrhagic cystitis
Rash
Jaw pain
Red coloured urine (doxorubicin – for up to 24 hours following administration)

Significant drug interactions – for full details consult product literature/ reference texts

Warfarin/coumarin anticoagulants: increased or fluctuating anticoagulant effects. Avoid if possible, consider switching patient to a low molecular weight heparin during treatment or if the patient continues taking an oral anticoagulant monitor the INR at least once a week and adjust dose accordingly.

Vincristine:
Itraconazole, voriconazole, posaconazole: increase severity of neuromuscular side effects. Avoid for 72 hours either side of vincristine dose if concurrent use cannot be avoided.

Cyclophosphamide:
Amiodarone: increased risk of pulmonary fibrosis – avoid if possible
Clozapine: increased risk of agranulocytosis – avoid concomitant use
Digoxin tablets: reduced absorption – give as liquid form
Indapamide: prolonged leucopenia is possible - avoid
Itraconazole: may increase adverse effects of cyclophosphamide
Phenytoin: reduced absorption - may need to increase dose of phenytoin
Grapefruit juice: decreased or delayed activation of cyclophosphamide. Patients should be advised to avoid grapefruit juice for 48 hours before and on day of cyclophosphamide dose.

Cytarabine:
Digoxin: cytarabine may affect plasma digoxin levels – consider monitoring

Additional comments

Doxorubicin has a life time maximum cumulative dose of 450mg/m^2

Leukaemogenic potential unknown but not insignificant

Fertility - it is very important the patient understands the potential risk of infertility. All patients should be offered fertility advice

References

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- Geisler CH, et al; Nordic Lymphoma Group. 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. 2008 Oct 1; 112 (7): 2687-93.
- Bunn and Ashley UK Renal Pharmacy Group The Renal Drug Handbook 1999
- Schrier and Gambertoglio Handbook of Drug therapy in Liver and kidney disease 1991
- UCLH - Dosage Adjustment for Cytotoxics in Hepatic Impairment (Version 3 - updated January 2009).
- UCLH - Dosage Adjustment for Cytotoxics in Renal Impairment (Version 3 - updated January2009).

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