

Cytarabine (high dose) +/- Rituximab

INDICATION

Relapsed mantle cell lymphoma.

TREATMENT INTENT

Disease modification.

PRE-ASSESSMENT

1. Ensure histology is confirmed prior to administration of chemotherapy and document in notes.
 2. Record stage of disease - CT scan (neck, chest, abdomen and pelvis), presence or absence of B symptoms, clinical extent of disease, bone marrow aspirate and trephine.
 3. Blood tests - FBC, DAT, U&Es, LDH, ESR, urate, calcium, magnesium, creatinine, LFTs, glucose, hepatitis B core antibody and hepatitis B surface Ag, hepatitis C antibody.
 4. Urine pregnancy test - before cycle 1 of each new chemotherapy course for women of child-bearing age unless they are postmenopausal, have been sterilised or undergone a hysterectomy.
 5. ECG +/- Echo - *if clinically indicated*.
 6. Record performance status
 7. Record height and weight.
 8. Consent - ensure patient has received adequate verbal and written information regarding their disease, treatment and potential side effects. Document in medical notes all information that has been given. Obtain written consent on the day of treatment.
 9. Fertility - it is very important the patient understands the potential risk of infertility. All patients should be offered fertility advice by referring to the Oxford Fertility Unit.
 10. Hydration - *in patients with bulky disease* pre-hydrate with sodium chloride 0.9% 1 litre over 4-6 hours. For patients at high risk of tumour lysis, refer to the tumour lysis protocol.
 11. Consider dental assessment / Advise dental check is carried out by patient's own dental practitioner before treatment starts.
 12. Treatment should be agreed in the relevant MDT.
 13. This chemotherapy regimen is usually delivered during an inpatient stay but can be used in ambulatory setting for patient(s) meeting criteria. Refer to local Ambulatory Care Operational Policy.
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DRUG REGIMEN

Day 1

Premedication

Paracetamol 1g PO, Chlorphenamine 10 mg IV, Hydrocortisone 100 mg IV.
Give 30 minutes before rituximab.

RITUXIMAB 375 mg/m² IV infusion in 500 mL sodium chloride 0.9%.
(Refer to rituximab protocol for titration of infusion rate. If first dose well tolerated, consider rapid infusion rituximab for dose 2 onwards).

Days 1-2

CYTARABINE 3 g/m² (NB: Consider reducing to 2 g/m² in the elderly or co-morbid) IV infusion **BD** in 250 mL sodium chloride 0.9% over 2 hours, i.e. 4 doses in total.

Doses can be administered via an ambulatory infusion pump. If the maximum flow rate of infusion pump is <125mL/hr, replace diluent with 100mL sodium chloride 0.9%.

CYCLE FREQUENCY

Cycle repeats every three weeks, support with G-CSF when necessary.

RESTAGING

Give 2 courses and restage with CT. If progressive disease, consider other treatment. If a response is seen, continue and restage after a total of 4-6 cycles.

DOSE MODIFICATIONS

The course should normally only be given if platelets > 100 x 10⁹/L and neutrophils > 1 x 10⁹/L.

Renal impairment		Hepatic impairment
GFR (mL/min)	Dose	Mild and Moderate: no formal dose adjustment required. Severe (defined as Childs-Pugh Class C or Bilirubin >3-10 x ULN): consider 25-50% of the original dose and increase if tolerated.
≥60	100%	
31-59	50%	
<30	Not recommended	

INVESTIGATIONS

FBC, renal and liver profiles.

CONCURRENT MEDICATION

Allopurinol	300 mg daily for 7 days starting 24-48 hours prior to
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	chemotherapy (first course / cycle only)
Aciclovir	200 mg three times a day for duration of treatment and for 3 months after completion
Prednisolone 0.5-1% eye drops Or Dexamethasone 0.1% eye drops (depending on local formulary)	One drop to each eye QDS. Continue for 5 days after cytarabine (due to risk of cytarabine-induced conjunctivitis). In the event of conjunctivitis, consider increasing the frequency to 2 hourly until resolution of symptoms. Liaison with ophthalmologists may be necessary in this situation.
G-CSF	Consider as per local protocol (start from Day 6 for 5-7 days if required).

EMETIC RISK

Days 1-2: Moderate.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

Rituximab - severe cytokine release syndrome is characterised by severe dyspnoea, often accompanied by bronchospasm and hypoxia, in addition to fever, chills, rigors, urticaria, and angioedema. Hepatitis B reactivation- see pathway for treatment and management of HBV positive patients.

Cytarabine - nausea, diarrhoea, oral ulceration, hepatic dysfunction, neuropathy, pulmonary toxicities, cardiomyopathy. A cytarabine syndrome is recognised in which patients suffer from: fever, myalgia, bone pain, occasional chest pains, maculopapular rash, conjunctivitis and malaise. It usually occurs 6 to 12 hours following administration. Cerebellar toxicity is also a recognised, albeit rare, side effect of high dose cytarabine.

EXTRAVASATION RISK

Cytarabine: neutral
 Rituximab: neutral

TREATMENT RELATED MORTALITY

Expected to be 1-2%.

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2. Forbes A, Farrell K, McKay P, Bolam S, Rule S. High dose cytarabine with rituximab is an effective first-line therapy for mantle cell lymphoma and produces ample stem cell harvest yields after multiple chemotherapy cycles. *Leuk Lymphoma*. 2013 Oct;54(10):2303-5.
3. The Lancet Oncology. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. *Lancet Oncol* 2019; 20:e201-08.
4. Hospira. Cytarabine Summary of Product Characteristics. Updated 26/04/2021. Accessed on 03/06/2021 via <http://www.medicines.org.uk/emc>.

Review

Name	Revision	Date	Version	Review date
Cheuk-kie Jackie Cheung (Pharmacist)	Pre-assessment section updated in line with other MTX protocol, ambulatory care information added.	Sep 2019	4.4	May 2020
Sara Castro (Advanced Haematology Pharmacist)	Annual Protocol Review	May 2021	1.5	May 2023

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