(R) DHAP - Cisplatin, Cytarabine and Dexamethasone +/- Rituximab

Indication

Salvage chemotherapy for relapsed/refractory Hodgkin's or Non-Hodgkin's Lymphoma

First line therapy in combination with alternating R-CHOP in patients with Mantle Cell Lymphoma with stage III/IV disease up to 65 years of age.

ICD-10 codes

Code with prefix C81-86

Regimen details

Day	Drug	Dose	Route
1-4	Dexamethasone	40mg	IV or PO
1*	Rituximab	375mg/m^2	IV infusion
1	Cisplatin	100mg/m^2	IV infusion
2	Cytarabine	2g/m^2 BD (12 hours apart)	IV infusion

*Rituximab for B cell Non Hodgkin's lymphoma patients only.

Consider starting GCSF (according to local policy, dose based on weight) either to shorten the duration of neutropenia (days 5-11) or to facilitate peripheral bloods stem cell collection (days 8-15).

Cycle frequency

Repeated every 21-28 days - as soon as blood counts recovered i.e. neutrophils >1.0 x 10^9/L and platelets (unsupported) >100x10^9/L (unless cytopenias related to disease).

Number of cycles

Relapse setting: 2 cycles - then reassess disease for suitability for consolidation with stem cell transplant.
Non-transplant eligible: up to 6 cycles (total).

Mantle cell lymphoma: 3 cycles alternating with R-CHOP followed by consolidation with autograft.

Administration

Day 1

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.

Cisplatin is administered in 1000mL sodium chloride 0.9% over 2 hours following the pre and post hydration as per protocol below:

Infusion Fluid & Additives	Volume	Infusion Time
Sodium Chloride 0.9%	1000mL	1 hour
Mannitol 20% OR Mannitol 10%	200mL 400mL	30 minutes 30 minutes
Ensure urine output > 100mL / hour prior to giving cisplatin. Give a single dose of furosemide 20mg IV if necessary.		
Cisplatin in Sodium Chloride 0.9%	1000mL	2 hours
Sodium Chloride 0.9% + 2g MgSO4 + 20mmol KCL	1000mL	2 hours
TOTAL	**3200mL or 3400mL**	**5 hours 30 minutes**

Additional pre hydration may be given as per local policy or required for individual patients.

Patients with low magnesium levels (< 0.7 mmol/L) should have an additional 2g magnesium sulphate added to the pre-hydration bag.

An accurate fluid balance record must be kept.

All patients must be advised to drink at least 2 litres of fluid over the following 24 hours.

Day 2
Cytarabine is administered in 1000mL sodium chloride 0.9% over 3 hours. Start time of each infusion must be 12 hours apart. A total of 2 doses are given.

Pre-medication

Rituximab premedication:

- Paracetamol 500mg-1g PO 30- 60 minutes prior to rituximab infusion
- Chlorphenamine 10mg IV bolus 15-30 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 dexamethasone has been taken at least 30 minutes prior to the start of the rituximab infusion)

Emetogenicity

This regimen has high emetic potential.

Additional supportive medication

Allopurinol 300mg OD (100mg OD if CrCl < 20mL/min) for the first 2 weeks.
Antiemetics as per local policy
Antiviral prophylaxis as per local policy.
Prophylactic antibiotics may be required e.g. ciprofloxacin (or as per local policy) when neutrophil count <0.5 x 10^9/L.
Consider antifungal and PCP prophylaxis as per local policy.
Mouthwashes as per local policy.
H_2 antagonist or proton-pump inhibitor if required.
Prednisolone 0.5% eye drops 1 drop QDS to both eyes (to avoid chemical conjunctivitis from high dose cytarabine) to start on day 2 for 5-7 days.
If magnesium/potassium levels < normal reference range, replace as per local policy.

Extravasation

Rituximab and cytarabine are neutral (Group 1)
Cisplatin is an exfoliant (Group 4)

Investigations – pre first cycle

Investigation	Validity period
FBC	14 days
U&Es	14 days
LFTs	14 days
Magnesium	14 days
Calcium	14 days

Other pre-treatment investigations:
Hepatitis B sAg & core antibody
Hepatitis C antibody
HIV antibody
Immunoglobulin levels (IgG, A, M)
HbA1c
LDH

Investigations – pre subsequent cycles

Investigation	Validity period
FBC	72 hours
U&Es	72 hours
LFTs	72 hours
Magnesium	72 hours
LDH	If clinically indicated

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

Investigation	Limit
Neutrophils	≥ 1.0 x 10^9/L
Platelets	≥ 100 x 10^9/L
Creatinine Clearance (CrCl)	≥ 60 mL/min
Bilirubin	< 1.5 x ULN

Unless cytopenias are disease related.

Dose modifications

- **Haematological toxicity**

There is no dose adjustment for haematological toxicity.

If neutrophils < 1.0 x 10^9/L and/or platelets (unsupported) < 100 x 10^9/L delay treatment until recovery (unless cytopenias are disease-related).

- **Renal impairment**

CrCl (mL/min)	Cisplatin dose
≥ 60	100%
45-59	75%
<45	Consider substitution with carboplatin

Consider omission of platinum at lesser renal impairment / ototoxicity in mantle cell lymphoma, as the most important component of the regimen is cytarabine.

CrCl (mL/min)	Cytarabine dose
> 60	100%
46-60	60%
31-45	50%
< 30	Omit/Contraindicated

- **Hepatic impairment**

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**

Cisplatin:

Toxicity	Definition	Cisplatin dose
Neurotoxicity including ototoxicity	≤Grade 1	100%
	Grade 2	50%
	Grade 3	Omit
	Grade 4	Discontinue
Stomatitis/Mucositis	Grade 1	100%
	Grade 2	Omit until ≤ grade 1 then 75% dose
	Grade 3	Omit until ≤ grade 1 then 50% dose
	Grade 4	Discontinue or omit until ≤ grade 1 then 50% dose

Toxicity	Definition	Cisplatin dose	Cytarabine dose
Other toxicities (except alopecia or nausea and vomiting)	Grade 3	Interrupt treatment until resolved then consider dose reduction	Interrupt treatment until resolved
	Grade 4	Interrupt treatment until resolved then consider dose reduction	75% dose

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

- **Serious side effects**

Myelosuppression
Infertility
Secondary malignancy
Anaphylactoid reaction
Nephrotoxicity
CNS toxicity (cytarabine)
Neurotoxicity including ototoxicity
Nephrotoxicity including electrolyte disturbance
Hepatotoxicity

- **Frequently occurring side effects**

Myelosuppression
Gastrointestinal toxicity
Rash
Conjunctivitis (cytarabine)
Arrhythmia

- **Other side effects**

Cytarabine syndrome (fever, myalgia, rash)

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.

Cisplatin:
Aminoglycoside antibiotics: increased risk of nephrotoxicity and ototoxicity when given within 2 weeks of cisplatin.
Diuretics: increased risk of nephrotoxicity and ototoxicity
Nephrotoxic drugs: increased nephrotoxicity ; not recommended
Ototoxic drugs: increased risk of ototoxicity
Phenytoin: cisplatin reduces absorption and efficacy of phenytoin, monitor levels and adjust dose as necessary.
Anti-gout agents: cisplatin may increase plasma concentration of uric acid therefore dose adjustments may be required to control hyperuricaemia and gout.
Lithium: cisplatin may affect lithium plasma levels – monitor.

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

Additional comments

Please refer to local guidelines if a patient has evidence of past or current hepatitis B infection.

References

- Summary of Product Characteristics Cytarabine (Hospira) accessed 16 Jan 2018 via www.medicines.org.uk
- Summary of Product Characteristics Cisplatin (Sandoz) accessed 16 Jan 2018 via www.medicines.org.uk
- Velasquez WS, Cabanillas F, Salvador P et al. Effective salvage therapy for lymphoma with cisplatin in combination with high dose Ara-C and Dexamethasone (DHAP). Blood 1988;71(1):117-122
- Delarue R et al. CHOP and DHAP plus rituximab followed by autologous stem cell transplantation (ASCT) in mantle cell lymphoma (MCL): a phase II study from the GELA. Blood 2013 121:48-53

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