CHOEP Therapy – 21 days

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Treatment of T-cell Non-Hodgkins Lymphoma (NHL)	C85	00396a	Hospital

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

Treatment is administered every 21 days for a maximum of 6 cycles or until disease progression or unacceptable toxicity develops.
Treatment can then be followed by BEAM (Ref NCCP Regimen 00408) and autologous transplant in suitable patients.

Facilities to treat anaphylaxis MUST be present when systemic anti-cancer therapy (SACT) is administered.

Table 1: Treatment Schedule for DOXOrubicin (IV), vinCRIStine (IV), Etoposide (IV), cycloPHOSphamide (IV) and prednisoLONE (PO)

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	[1]DOXOrubicin	50mg/m^2	IV Bolus over 15 mins	Into the side arm of a fast running 0.9% NaCl infusion	1-6
1	[2]vinCRIStine	1.4mg/m^2 (Max 2mg)	IV infusion	50ml minibag 0.9% NaCl over 15 minutes	1-6
1-3	Etoposide	100mg/m^2	IV infusion*	1000mls 0.9% NaCl or over 60 minutes	1-6
1	cycloPHOSphamide	750mg/m^2	IV infusion[3]	250mL 0.9% NaCl over 30 minutes	1-6
1-5	prednisoLONE[4]	100mg	PO		1-6
[1]Lifetime cumulative dose of DOXOrubicin is 450mg/m^2 **In establishing the maximal cumulative dose of an anthracycline, consideration should be given to the risk factors below[i] and to the age of the patient**					
[2] vincCRIStine is a neurotoxic chemotherapeutic agent. Refer to NCCP Guidance on the Safe Use of Neurotoxic drugs (including Vinca Alkaloids) in the treatment of cancer here					
[3] cycloPHOSphamide may also be administered as an IV bolus over 5-10 mins.					
[4] Alternative steroid regimens may be used at consultant discretion.					

*See alternate treatment schedule using IV and PO etoposide below.

ALTERNATE TREATMENT SCHEDULE: Etoposide Day 1 IV, Days 2 & 3 PO

Treatment is administered, as detailed in Table 2 below, every 21 days for a maximum of 6 cycles or until disease progression or unacceptable toxicity develops. To note, etoposide is administered as an IV infusion on Day 1 and then administered as PO doses on Days 2 and 3.
Treatment can then be followed by BEAM (Ref NCCP Regimen 00408) and autologous transplant in suitable patients.

Table 2: Treatment Schedule for DOXOrubicin (IV), vinCRIStine (IV), Etoposide (Day 1 IV, Days 2&3 PO), cycloPHOSphamide (IV) and prednisoLONE (PO)

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	[1]DOXOrubicin	50mg/m^2	IV Bolus over 15 mins	Into the side arm of a fast running 0.9% NaCl infusion	1-6
1	[2]vinCRIStine	1.4mg/m^2 (Max 2mg)	IV infusion	50ml minibag 0.9% NaCl over 15 minutes	1-6
1	Etoposide	100mg/m^2	IV infusion	1000mls 0.9% NaCl or over 60 minutes	1-6
1	cycloPHOSphamide	750mg/m^2	[3]IV infusion	250mL 0.9% NaCl over 30 minutes	1-6
1-5	[4]prednisoLONE	100mg	PO		1-6
2,3	Etoposide	[5]100mg/m^2 twice daily	PO		1-6
[1]Lifetime cumulative dose of DOXOrubicin is 450mg/m^2 **In establishing the maximal cumulative dose of an anthracycline, consideration should be given to the risk factors below[i] and to the age of the patient.**					
[2] vincRIStine is a neurotoxic chemotherapeutic agent. Refer to NCCP Guidance on the Safe Use of Neurotoxic drugs (including Vinca Alkaloids) in the treatment of cancer here					
[3] cycloPHOSphamide may also be administered as an IV bolus over 5-10mins.					
[4] Alternative steroid regimens may be used at consultant discretion.					
[5] Etoposide is available in 50mg and 100mg capsules. The capsules should be taken on an empty stomach.					

ELIGIBILITY:

- Indications as above
- Age < 60 years
- Adequate haematological, renal and liver status

EXCLUSIONS:

- Hypersensitivity to DOXOrubicin, cycloPHOSphamide, etoposide, vinCRIStine sulphate or any of the excipients
- A cumulative life-long dose of 450mg/m^2 of DOXOrubicin should only be exceeded with extreme caution as there is as risk of irreversible congestive heart failure
- Severe liver impairment (etoposide)
- Pregnancy
- Lactation

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist or by a Consultant Haematologist working in the area of haematological malignancies.

TESTS:

Baseline tests:

- FBC, renal and liver profile, LDH, blood glucose
- ECG
- MUGA or ECHO should be considered prior to the administration of DOXOrubicin in high-risk patients
- Virology screen - Hepatitis B (HBsAg, HBcoreAb) & C, HIV

*See Adverse Effects/Regimen Specific Complications re Hepatitis B Reactivation

Regular tests:

- FBC, renal and liver profile, LDH prior to each cycle
- Evaluate for peripheral neuropathy prior to each cycle
- Cardiac function if clinically indicated

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant
- Consider vinCRIStine dose reduction in elderly patients

Haematological:

Table 3: Recommended dose modification in haematological toxicity

ANC x 10^9/L		Platelets x 10^9/L	Dose modification
< 1	and/or	< 75	Dose modification not generally indicated. Consider treatment delay and/or add G-CSF.

Renal and Hepatic Impairment:

Table 4: Recommended dose modification in renal and hepatic impairment

Drug	Renal Impairment		Hepatic Impairment			
cycloPHOSphamide	**CrCl (ml/min)**	**Dose**	Severe impairment: Clinical decision.			
	>20	100%				
	10-20	75%				
	<10	50%				
DOXOrubicin	No dose reduction required. Clinical decision in severe impairment.		**Total Bilirubin (micromol/L)**			**Dose**
			20-51			50%
			51-85			25%
			>85			Omit
			If AST 2-3 x ULN give 75% dose If AST > 3 x ULN give 50% dose			
vinCRISTine	No dose modification required.		**Total Bilirubin (micromol/L)**		**AST/ALT Units**	**Dose**
			26-51	or	60-180	50%
			>51	and	Normal	50%
			>51	and	>180	omit
Etoposide	**CrCl (ml/min)**	**Dose**	**Total Bilirubin (micromol/L)**		**AST**	**Dose**
	>50	100%	26-51	or	60-180	50%
	15-50	75%	>51	or	>180	Clinical decision
	<15	50%				
	Subsequent doses should be based on clinical response.					

Management of adverse events:

Table 5: Recommended dose modification of vinCRIStine based on neurotoxicity (CTCAE v4.0)

Symptom	Dose of vinCRIStine
Grade 1	100%
Grade 2	Hold until recovery then reduce dose by 50%
Grade 3, 4	Omit

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

DOXOrubicin/cycloPHOSphamide: High (**Refer to local policy).**
vinCRIStine : Minimal (**Refer to local policy).**
Etoposide : Low (**Refer to local policy).**

- Consider increased risk of vinca alkaloid-induced adverse effects due to inhibition of CYP3A4 by aprepitant.

PREMEDICATIONS: Not usually required unless the patient has had a previous hypersensitivity.

OTHER SUPPORTIVE CARE:

- G-CSF prophylaxis may be required, please discuss with consultant.
- Tumour lysis syndrome prophylaxis – consider use of allopurinol 300mg daily for the first cycle **(Refer to local policy)** .
- PJP prophylaxis **(Refer to local policy).**
- Anti-viral prophylaxis **(Refer to local policy).**
- Anti-fungal prophylaxis (Avoid the concurrent use of azoles and vinCRIStine **(Refer to local policy).**
- Prophylactic regimen against vinCRIStine induced constipation is recommended **(Refer to local policy)**.
- Proton pump inhibitor while on prednisoLONE **(Refer to local policy).**
- Patients should have an increased fluid intake of 2-3 litres on day 1 to prevent haemorrhagic cystitis associated with cycloPHOSphamide.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

- **Hepatitis B Reactivation:** Patients should be tested for both HBsAg and HBcoreAb as per local policy. If either test is positive, such patients should be treated with anti-viral therapy **(Refer to local infectious disease policy).** These patients should be considered for assessment by hepatology.

vinCRIStine

- **Neuropathy:** vinCRIStine may cause peripheral neuropathy which is dose related and cumulative, requiring monitoring before each dose is administered. The presence of pre-existing neuropathies or previous treatment with other neurotoxic drugs may increase risk of peripheral neuropathy. Patients with mild peripheral neuropathy can usually continue to receive full doses of vinCRIStine, but when symptoms increase in severity and interfere with neurologic function, dose reduction or discontinuation of the drug may be necessary. The natural history following discontinuation of treatment is gradual improvement, which may take up to several months. A routine prophylactic regimen against constipation is recommended for all patients receiving vinCRIStine sulphate. Paralytic ileus may occur. The ileus will reverse itself upon temporary discontinuance of vinCRIStine and with symptomatic care.

DOXOrubicin

- **Cardiac Toxicity:** DOXOrubicin is cardiotoxic and must be used with caution, if at all, in patients with cardiac dysfunction.
- **Extravasation**: DOXOrubicin and vinCRIStine cause pain and possible tissue necrosis if extravasated (**Refer to local policy).**

DRUG INTERACTIONS:

- DOXOrubicin cardiotoxicity is enhanced by previous or concurrent use of other anthracyclines, or other potentially cardiotoxic drugs (e.g. 5-Flourouracil, cycloPHOSphamide or PACLitaxel) or with products affecting cardiac function (e.g. calcium antagonists).
- Consider increased risk of vinca alkaloid-induced adverse effects due to inhibition of CYP3A4 by aprepitant.

- Current drug interaction databases should be consulted for more information including potential for interactions with CYP3A4 inhibitors / inducers.

REFERENCES:

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12. vinCRIStine Summary of Product Characteristics. Accessed Jan 2023. Available at https://www.medicines.ie/medicines/vincristine-sulphate-1-mg-ml-solution-for-injection-or-infusion-34195/spc

Version	Date	Amendment	Approved By
1	08/03/2017		Prof Elisabeth Vandeberghe Prof Maccon Keane
2	27/03/2019	Updated to new NCCP template Standardized treatment table	Prof Elisabeth Vandeberghe Prof Maccon Keane

		Updated dosing modifications in hepatic impairment	
3	12/05/2021	Updated recommendation for hepatic impairment Updated adverse events section	Prof Maccon Keane
4	27/10/2023	Updated treatment table order of admin, and added alternate treatment schedule for oral etoposide. Updated emetogenic potential and drug interactions sections.	Prof Maccon Keane, Prof Elisabeth Vandenberghe

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] Cardiotoxicity is a risk associated with anthracycline therapy that may be manifested by early (acute) or late (delayed) effects.

Risk factors for developing anthracycline-induced cardiotoxicity include:
- high cumulative dose, previous therapy with other anthracyclines or anthracenediones
- prior or concomitant radiotherapy to the mediastinal/pericardial area
- pre-existing heart disease
- concomitant use of other potentially cardiotoxic drugs

In establishing the maximal cumulative dose of an anthracycline, consideration should be given to the risk factors above and to the age of the patient.