Escalated Dose BEACOPDAC 21 Day Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
Treatment of patients with high risk, advanced stage Hodgkin Lymphoma (IPS ≥ 3)	C81	00837a	N/A
Escalation of treatment of patients with Hodgkin Lymphoma after failure to reach complete metabolic response post 2 cycles of ABVD	C81	00837b	N/A

*For post 2012 indications only

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 patient's individual clinical circumstances.

The treatment is administered every 21 days for 4 cycles unless disease progression or unacceptable toxicity develops. This can be increased to 6 cycles at the consultant's discretion.
Facilities to treat anaphylaxis MUST be present when systemic anti-cancer therapy (SACT) is administered.

Day	Drug	Dose	Route	Diluent and Rate
1	[a]cycloPHOSphamide	1250mg/m^2	IV infusion	250mL 0.9% NaCl over 30 minutes
1	[b]DOXOrubicin	35mg/m^2	IV Bolus	Slow IV bolus over 15 minutes with 0.9% NaCl
1,2,3	[c]Etoposide	200mg/m^2	IV infusion	1000mL 0.9% NaCl over 2 hours
2,3	[d]Dacarbazine	250mg/m^2 once daily	IV infusion	250mL NaCl 0.9% over 30 minutes
8	[e]vinCRIStine	1.4mg/m^2 (cap at 2mg)	IV infusion	50mL 0.9% NaCl over 15 minutes
8	[f]Bleomycin	10,000IU International units/ m^2	IV Bolus	Into the side arm of a fast running 0.9% NaCl infusion
1-14	[g]prednisoLONE	40mg/m^2 once daily	PO	
9-13 approx	G-CSF (Round to nearest whole syringe)	5 micrograms/kg	SC	until ANC >1x10^9/L for 3 days
[a]Consideration could be given to the administration of MESNA 250mg/m^2 IV at T0, T+4 and T+8hr after administration of the cyclophosphamide at the discretion of the prescribing consultant.				
[b]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 outlined below[i] and to the age of the patient.**				
[c] The etoposide 200mg/m^2 dose may need to be split into two 1000mL bags for stability reasons. These should be administered sequentially.				
[d]Dacarbazine is sensitive to light exposure. All reconstituted solutions should be suitably protected from light also during				

administration (light-resistant infusion set).
[e]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.
[f]The total cumulative dose of bleomycin should NOT exceed 400,000 international units. The risk of pulmonary toxicity increases beyond a cumulative dose of 300,000 international units. Check the cumulative dose prior to each treatment. Bleomycin dosing should only be expressed in terms of international units.
[g]Alternative steroid regimens with tapering doses may be used at consultant discretion, **e.g.** 60mg od for 14 days, 40mg od for 2 days, 20mg od for 2 days, 15mg od for 1 day, 10mg od for 1 day, 5mg od for 1 day-,then, stop (21 days in total). prednisoLONE is taken as a single daily dose in the morning.

ELIGIBILITY:

- Indications as above
- ECOG status 0-2

CAUTIONS:

- Patients ≥60 should be treated at the discretion of the prescribing Consultant

EXCLUSIONS:

- Hypersensitivity to cycloPHOSphamide, DOXOrubicin, etoposide, vinCRIStine, bleomycin dacarbazine, prednisoLONE or any of the excipients.
- Bleomycin is contraindicated in patients with acute pulmonary infection or chest X rays suggesting diffuse fibrotic changes or impaired lung function
- Severe liver or kidney impairment
- Leucopenia and/or thrombocytopenia
- Breast feeding
- Pregnancy

PRESCRIPTIVE AUTHORITY:

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

TESTS:

Baseline tests:

- FBC, renal and liver profile
- ECG
- Cardiac function using MUGA or ECHO (LVEF > 50% required to administer doxorubicin) if clinically indicated (e.g. smoking history, hypertension).
- Pulmonary function tests (PFTs) prior to bleomycin
- Virology screen - Hepatitis B (HBsAg, HBcoreAb), Hepatitis C, HIV
  *See Adverse Effects/Regimen Specific Complications re Hepatitis B Reactivation

Regular tests:

- FBC, renal and liver profile prior to each cycle on day 1
- Chest x-ray +/- PFTs, as clinically indicated
- If clinically indicated, MUGA scan or echocardiogram

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:

- Full dose intensity should be maintained where possible.
- Dose modification should only be carried out following discussion and approval by the consultant.

Haematological:

Table 1: Haematological criteria to proceed with next cycle of treatment

	ANC		Platelets	Recommendation
Day 1	>1.0 X 10^9/L	and	> 80 X 10^9/L	Cycle proceeds

- If these values are not reached on day 1 of the next scheduled cycle of treatment, therapy is deferred and FBC should be checked again after 3, 7, 10 and 14 days or until blood count recovery.
- Bleomycin and vinCRIStine should be administered on schedule and at full dose even if leucopenia is observed on day 8.

Dose modifications (De-escalation as per HD15 protocol, Engert et al)
There is a predefined scheme for dose de-escalation for BEACOPDAC Escalated Therapy.
Ensure to discuss with consultant prior to implementing dose modifications as dose intensity should be maintained where possible

- The dose in all subsequent cycles will be reduced by one dose level should one or more toxic events occur in a given cycle (see Table 2 below).
- If any toxic event occurs in 2 successive cycles, the subsequent cycle is administered at baseline dose.
- Once dose levels have been reduced, they are not re-escalated for subsequent cycles.

Consider requirement for dose reduction (as per Table 2 below) for the following toxic events.
Toxic events include:
  - Grade 4 neutropenia or thrombocytopenia
  - Grade 4 leucopenia for more than 4 days (White cell count < 1 x 10^9/L)
  - Other grade 4 toxicity

Table 2: Dose reduction levels for Escalated BEACOPDAC

Level	Cyclophosphamide (Day 1)	DOXOrubicin (Day 1)	Etoposide (Day 1)
*4	1250 mg/m^2	35 mg/m^2	200 mg/m^2
3	1100 mg/m^2	35 mg/m^2	175 mg/m^2
2	950 mg/m^2	35 mg/m^2	150 mg/m^2
1	800 mg/m^2	35 mg/m^2	125 mg/m^2
Baseline	650 mg/m^2	25 mg/m^2	100 mg/m^2

*Starting Level

Renal and Hepatic Impairment:

Table 3: Recommended dose modifications based on renal and hepatic impairment

Drug	Renal Impairment		Hepatic Impairment	
cycloPHOSphamide	**CrCl (mL/min)**	**Dose**	Mild and moderate: no need for dose adjustment is expected. Severe: not recommended, due to risk of reduced efficacy	
	≥30	No dose adjustment is needed		
	10-29	Consider 75% of the original dose		
	<10	Not recommended, if unavoidable consider 50% of the original dose		
	Haemodialysis	Not recommended, if unavoidable consider 50% of the original dose		
Bleomycin	**CrCl (mL/min)**	**Dose**	No need for dose adjustment is expected	
	>50	No dose adjustment is needed		
	10-50	75% of original dose		
	<10	50% of original dose		
	Haemodialysis	50% of the original dose may be considered		
DOXOrubicin	**CrCl (mL/min)**	**Dose**	**Bilirubin (micromol/L)**	**Dose**
	>10	No dose adjustment is needed	20-50	50% of the original dose
	<10	No need for dose adjustment is expected	51-86	25% of the original dose
	Haemodialysis	75% of the original dose may be considered	>86 or Child-Pugh C	Not recommended

Etoposide	**CrCl (mL/min)**	**Dose**	Bilirubin < 50 µmol/L **and** normal albumin **and** normal renal function: no need for dose adjustment is expected Bilirubin ≥ 50 µmol/L **or** decreased albumin levels: consider 50% of the dose, increase if tolerated
	>50	No dose adjustment is needed	
	10-50	75% of the original dose, increase if tolerated	
	Haemodialysis	Not dialysed, consider 75% of the original dose	
Dacarbazine	**CrCl (mL/min)**	**Dose**	Can be hepatotoxic. Consider dose reduction.
	45-60	80%	
	30-45	75%	
	<30	70%	
vinCRIStine	Renal impairment: no need for dose adjustment is expected Haemodialysis: no need for dose adjustment is expected		Bilirubin > 51 µmol/l: 50% of original dose
cycloPHOSphamide, bleomycin, DOXOrubicin, etoposide, vinCRIStine – renal and hepatic: Giraud et al 2023 Dacarbazine - Renal and hepatic: North London Cancer Network 2009			

Neurotoxicity:

Table 4: Dose modification of vinCRIStine based on neurotoxicity (CTCAE v 4.0)

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

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

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

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

PREMEDICATIONS:

None usually required

OTHER SUPPORTIVE CARE:

- Tumour lysis syndrome prophylaxis **(Refer to local policy)**
- Proton pump inhibitor **(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)**
- Patients should have an increased fluid intake of 2-3 litres on day 5 to prevent haemorrhagic cystitis associated with cycloPHOSphamide.
- All patients should receive irradiated blood products – **Refer to local policy** for notification procedure
- Consider referral for fertility preservation

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

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

- **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated appropriately.
- **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.
- **Extravasation:** vincristine, DOXOrubicin and dacarbazine cause pain and possible tissue necrosis if extravasated **(Refer to local policy)**.

DOXOrubicin

- **Cardiotoxicity:** DOXOrubicin is cardiotoxic and must be used with caution, if at all, in patients with severe hypertension or cardiac dysfunction.

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.
- **Constipation:** 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.

Bleomycin

- **Pulmonary toxicity**: Bleomycin may cause severe and life threatening pulmonary toxicity. Pulmonary toxicity of bleomycin is both dose-related and age-related. It may also occur when lower doses are administered, especially in elderly patients; in patients with reduced kidney function, pre-existing lung disease, previous or concurrent radiotherapy to the chest and in patients who need administration of oxygen. It is significantly exacerbated by thoracic radiation and by hyperoxia used during surgical anaesthesia. Smoking is also a risk factor.

Dacarbazine

- **Hepatotoxic drugs** and alcohol should be avoided during chemotherapy.
- **Vein Irritation**: Dacarbazine often causes pain during administration that usually responds to slowing the infusion rate.

DRUG INTERACTIONS:

- CYP3A4 inducers may increase the clearance of etoposide.
- CYP3A4 and p-gp inhibitors may decrease the clearance of etoposide.
- Bleomycin causes sensitisation of lung tissue to oxygen. If oxygen is required, the use of low concentration (e.g. 25%) is recommended. Fluid replacement should be carefully monitored.
- Dacarbazine is metabolised by cytochrome P450 (CYP1A1, CYP1A2, and CYP2E1). This has to be taken into account if other medicinal products are co-administered which are metabolised by the same hepatic enzymes.
- Concomitant use of phenytoin and dacarbazine should be avoided since there is a risk of exacerbation of convulsions resulting from the decrease of phenytoin digestive absorption.
- 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:

1. Borchmann P et al. PET- guided treatment in patients with advanced stage Hodgkins Lymphoma (HD18): Final results of an open-label, international, randomised, phase III trial by the German Hodgkin Study Group. Lancet 2017; 390: 2790-802.
2. Mauz-Körholz, C et al. Procarbazine-free OEPA-COPDAC chemotherapy in boys and standard OPPA-COPP in girls have comparable effectiveness in pediatric Hodgkin's lymphoma: the GPOH-HD-2002 study. J Clin Oncol, 28(23), 3680-3686.
3. Engert A, Haverkamp H et al. Reduced-intensity chemotherapy and PET-guided radiotherapy in patients with advanced stage Hodgkin's lymphoma (HD15 trial): a randomised, open-label, phase 3 non-inferiority trial. Lancet. 2012;379(9828):1791-9
4. Dosage Adjustment for Cytotoxics in Renal Impairment January 2009; North London Cancer Network.
5. Dosage Adjustment for Cytotoxics in Hepatic Impairment January 2009; North London Cancer Network.
6. Giraud E L, Lijster B D, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment: an update. Available at: https://pubmed.ncbi.nlm.nih.gov/37269847/

7. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V5 2023. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf
8. Vinca alkaloids + Azoles. Stockley's Drug Interactions 11th Edition
9. cycloPHOSphamide (Endoxana®) Injection 500mg Powder for Solution for Injection. Summary of Product Characteristics. Last updated 21/12/2018. Accessed Jan 2024. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2299-027-001_21122018112107.pdf
10. DOXOrubicin 2mg/mL. Summary of Product Characteristics. Last updated 26/02/2020. Accessed Jan 2024. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2315-083-001_26022020112618.pdf
11. Etoposide Summary of Product Characteristics. Last updated 17/05/2021. Accessed Jan 2024. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2059-036-001_17052021114619.pdf
12. vinCRIStine 1mg/mL Solution for Injection or Infusion Summary of Product Characteristics. Last updated 09/10/23. Accessed Jan 2024. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA0822-232-001_09102023163547.pdf
13. Bleomycin 15,000 IU Powder for Injection or Infusion Summary of Product Characteristics. Accessed Jan 2024. Available at https://www.hpra.ie/img/uploaded/swedocuments/LicenseSPC_PA0937-008-001_27022007022417.pdf
14. Dacarbazine 1000mg Powder for Solution for Infusion Summary of Product Characteristics. Last updated 09/08/2022. Accessed Jan 2024. Available at https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA1760-001-003_09082022114457.pdf

Version	Date	Amendment	Approved By
1	20/05/2024		NCCP Lymphoid SACT CAG

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