BEACOPDac - Escalated

[This protocol has replaced Escalated BEACOPP in view of data demonstrating possible reduced toxicity and comparable effectiveness of dacarbazine compared to procarbazine]

INDICATION

HODGKIN LYMPHOMA (HL) [ICD-10 code: C.81]

- **Licensed / NHSE funded**

  - **Early Stage Classical Hodgkin Lymphoma**
    1. For early unfavourable / intermediate stage (specifically excluding stage IIB with bulk and / or E lesions), consider 2 x escBEACOPDac with 2x ABVD (HD17 approach)
    2. Alternatively, can use 2 x escBEACOPDac after a positive interim PET (Deauville 4 or 5) following 2 x ABVD (either early favourable or unfavourable / intermediate stage)

  - **Advanced Classical Hodgkin lymphoma**
    1. Either as initial therapy with a plan for 4 cycles if interim PET negative; 6 cycles if interim PET positive (alternatively, can de-escalate to 4x A(B)VD if interim PET negative)
    2. Alternatively, 4 cycles in those with a positive interim PET-CT (Deauville 4 or more) after 2 cycles of ABVD

This protocol should normally be restricted to patients with WHO performance status 0-2, and aged 60 or younger (caution in those 50 years of age and over). Initiation of BEACOPDac - Escalated protocol should only be undertaken after discussion at the lymphoma MDT.

TREATMENT INTENT

Curative

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) and / or PET-CT scan, presence or absence of B symptoms and clinical extent of disease.
3. If PET-CT scan is performed at diagnosis, routine bone marrow is generally not required.
4. **Pulmonary function** if clinically indicated (refer to the **Bleomycin supportive care document [Link]**)
5. Blood tests - FBC, ESR, U&Es, LDH, urate, calcium, magnesium, creatinine, LFTs, glucose, Igs, Hepatitis B core antibody, Hepatitis B surface Ag, Hepatitis C antibody, EBV, CMV, VZV, HIV 1+2 after consent.
6. **Send a "group and save" sample to transfusion and inform patient and transfusion laboratory that they will require irradiated blood products for all future transfusions**. Ensure irradiation card is attached to the patient's notes. See 'Guidelines for the use of blood components in adult haematology' [Link].
7. Urine pregnancy test - before each course of chemotherapy for women of child-bearing age unless they are postmenopausal, have been sterilised or undergone a hysterectomy.

8. ECG +/- Echo - *if clinically indicated*.
9. Record performance status (WHO/ECOG), height and weight.
10. 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 prior to treatment.
11. Fertility - it is very important the patient understands the potential risk of reduced fertility. All patients should be offered fertility advice by referring to the Oxford Fertility Unit.
12. Hydration - *in patients with bulky disease* pre-hydrate with sodium chloride 0.9% 1 litre over 4-6 Assess and document tumour lysis risk as part of pre-assessment. Refer to the Tumour Lysis Syndrome in Adults protocol (H.8).
13. Consider dental assessment / Advise dental check is carried out by patient's own dental practitioner before treatment starts.
14. **Placement of a central line / PICC is highly recommended.**

DRUG REGIMEN

Consider at consultant discretion:

- steroid pre-phase (e.g., dexamethasone 40 mg daily) for 4 days prior to treatment in patients aged 40 or older and up to 7 days in younger patients

Day(s)	Drug	Dose	Route	Administration details
1	**DOXORUBICIN**	35mg/m^2	IV bolus	
1	MESNA	250mg/m^2	IV bolus	[Administered at the same time as cyclophosphamide. Further doses to be given orally 2 and 6 hours post cyclophosphamide – see *CONCURRENT MEDICATIONS*]
1	**CYCLOPHOSPHAMIDE**	1250mg/m^2	IV infusion	in 250mL sodium chloride 0.9% over 30 minutes (or slow IV blous) [Patient should also drink 3L of fluid on the day of cyclophosphamide]
1–3	**ETOPOSIDE**	200mg/m^2 OD	IV infusion	in 1000mL sodium chloride 0.9% over 1 hour [concentration 0.05–4mg/ml]
2–3	**DACARBAZINE**	250mg/m^2 OD	IV infusion	in 1000mL sodium chloride 0.9% over 1 hour [concentration 0.32–4mg/ml]
1–14	**PREDNISOLONE**	40mg/m^2 OD	PO	Take in the morning, with or just after food
8	**BLEOMYCIN**	10,000 International Units/m^2	IV infusion	in 100mL sodium chloride 0.9% over 1 hour
8	**VINCRISTINE**	1.4mg/m^2 [max. 2mg]	IV infusion	in 50mL sodium chloride 0.9% over 15 minutes
4-7 and 9-12$^{\alpha}$	**FILGRASTIM$^{\beta}$**	0.5 million units/kg OD	SC	$^{\alpha}$or until blood counts recovered $^{\beta}$or equivalent G-CSF as per local formulary
CYCLE FREQUENCY: 21 days				
DURATION: 2 – 6 cycles				

RESTAGING

- Clinical assessment prior to each course.

For early or intermediate stage patients:

1. If following an HD17 approach (early unfavourable / intermediate stage patients), give 2 cycles as initial therapy and then 2 cycles of ABVD. Although not in the trial, an interim PET is recommended after the 2 cycles of escalated BEACOPDac prior to ABVD. If positive, discuss at MDT. .
2. If following an HD10 approach, consider giving only 2 courses of Escalated BEACOPDac for those who are interim PET positive after 2 cycles of ABVD, followed by radiotherapy[3].

For advanced stage patients:

1. If following an HD18 approach, Escalated BEACOPDac can be used as frontline therapy after a discussion with the patient regarding risk versus benefit. An interim PET-CT scan is recommended after 2 cycles. If the PET is negative (Deauville 1-3), 2 more cycles should be given; if the PET is negative (Deauville 1-3), 2 more cycles should be given; if the PET is positive (Deauville 4-5), 4 more cycles should be given, the PET repeated and radiotherapy applied to any residual masses of 2.5cm or more which are PET avid.
2. If following a RATHL approach (after a positive interim PET with ABVD), further PET recommended after 3 cycles of BEACOPDac-Escalated. If negative, recommend 1 further cycle of BEACOPDac-Escalated[2]. Optimum timing of the scan is D11 or more after the start of the cycle.

DOSE MODIFICATIONS

1. HAEMATOLOGICAL TOXICITIES

Cycle 1: Full dose chemotherapy should be given.

Cycle 2 and subsequent courses: Proceed with chemotherapy provided the white cell count > 2.5 x10^9/L and the platelet count > 80x10^9/L.

No dose reductions due to haematological toxicities are required for dacarbazine, prednisolone, bleomycin and vincristine.

Doxorubicin, cyclophosphamide and etoposide:

- Doses should be reduced if one or more adverse event occurs following the previous cycle. Treatment always begins at cycle 1 at level 4, i.e., at starting (escalated) doses **(Table 1)**. Doses are not to be escalated back once reduced.

- **Adverse events (CTCAE v5.0) include:**
  - Grade 4 leukopenia (WBC < 1.0 x 10^9/L) for more than four days,
  - Grade 4 thrombocytopenia on one or more days (platelets < 25 x 10^9/L),
  - Grade 4 infection, mucositis, or any other grade 4 toxicities
  - Delay of treatment by two-weeks or more due to inadequate blood counts recovery

- If any adverse event (CTCAE v5.0) occurs in two consecutive cycles, standard doses should be used for all subsequent cycles (**Table 1**).

Table 1. BEACOPDac doses de-escalation scheme.

Level	Doses (mg/m²) on day 1		
	Doxorubicin	Cyclophosphamide	Etoposide
4* Starting (escalated) doses	35	1250mg	200
3	35	1100	175
2	35	950	150
1	35	800	125
Standard doses	25	650	100

2. NON-HAEMATOLOGICAL TOXICITIES:

Neurotoxicity and gastro-intestinal disorders:
If the patient complains of significant constipation or sensory loss in fingers and/or toes, consider possible dose reduction of vincristine. For patients who develop ≥ Grade 3 ileus, treatment should be delayed until recovery and vincristine introduced at 75% of the normal dose thereafter. If ≥ Grade 3 ileus recurs, vincristine should be discontinued.

Pulmonary toxicity
All patients complaining of shortness of breath should have a CXR (also consider HRCT chest) and consider pulmonary function tests prior to further administration of bleomycin. Bleomycin should be discontinued if any clinical signs or CXR evidence of pulmonary infiltration/fibrosis develop, or if the transfer factor is <50% of the predicted value.

Recommended total maximum cumulative dose of bleomycin: 225,000 international units (lymphoma patients)

Cardiac toxicity
Consider doxorubicin cardiotoxicity and the maximum lifetime anthracycline exposure for dose modifications. Doxorubicin must be used with caution, if at all, in patients with cardiac dysfunction. Discuss with consultant.

Recommended total maximum cumulative dose of doxorubicin (additive to other anthracyclines): 400-450 mg/m²

Renal / Hepatic Impairment

	Renal impairment	Hepatic impairment
Doxorubicin	GFR > 10 mL/min: 100% dose GFR < 10 mL/min: no need for dose adjustment is expected, clinical decision	Bilirubin 20-50 µmol/L: 50%dose Bilirubin 51 µmol/L– 86 µmol/L: 25% dose Bilirubin > 86 µmol/L or Child-Pugh C: not recommended

	Renal impairment	Hepatic impairment
Cyclophosphamide	GFR ≥30 mL/min: 100% dose GFR 10-29 mL/min: 75% dose GFR < 10 mL/min: omit [consider 50% dose if unavoidable]	Mild and moderate: 100% dose Severe: 75% dose if bilirubin > 53 µmol/L or omit, due to risk of reduced efficacy
Etoposide	GFR > 50 mL/min: 100% dose GFR 15-50 mL/min: 75% dose, increase if tolerated GFR < 15 mL/min: no data, clinical decision	Bilirubin < 50 µmol/L and normal albumin and normal renal function: 100% dose Bilirubin ≥ 50 µmol/L or decreased albumin levels: consider 50% dose, increase if tolerated
Dacarbazine	GFR ≥ 30 mL/min without hepatic impairment: 100% dose GFR < 30 mL/min: consider 70% dose	Mild and moderate without renal impairment: 100% dose Severe: not recommended
Bleomycin	GFR > 50 ml/min: 100% dose GFR 10-50 ml/min: 75% dose GFR < 10 ml/min: 50% dose	No need for dose adjustment is expected, clinical decision
Vincristine	No need for dose adjustment is expected, clinical decision	Bilirubin > 51 µmol/l: 50% dose

CONTRAINDICATIONS

Refer to individual medications Summary of Product Characteristics (SmPCs)
Vincristine – for intravenous use only; fatal if given by other routes

INVESTIGATIONS

- FBC, U&Es, LFTs prior to Days 1 and 8.
- Closer monitoring is often necessary during BEACOPDac-escalated therapy as profound cytopenia is common (monitor blood tests 1 – 2 times / week).

CONCURRENT MEDICATIONS

Allopurinol	300mg daily for 7 days [Cycle 1 only] unless otherwise indicated in TLS risk assessment. Refer to the Tumour Lysis Syndrome in Adults protocol (H.8)
Proton pump inhibitor (as per local formulary)	Omeprazole 20mg once daily for the duration of treatment
Fluconazole	50mg daily for the duration of treatment
Aciclovir	200mg three times a day for duration of treatment and for 3 months after completion
Mesna	Mesna IV bolus (administered immediately before cyclophosphamide infusion – see DRUG REGIMEN section), followed by oral mesna (500mg/m^2) administered at 2 and 6 hours after the intravenous mesna dose. 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.

Co-trimoxazole	480mg OD on Mon / Wed / Fri for duration of treatment and for 3 months afterwards (consider reducing the dose to 480 mg twice weekly during neutropenic periods)
Filgrastim (or equivalent G-CSF as per local formulary)	0.5 million units/kg SC OD from days 4-7 and then days 9-12 (see DRUG REGIMEN section)
Bone protection (consider for patients >50 years)	See "Bone Protection in Lymphoma" supportive care guidance [Link] regarding Calcium supplementation and use of Zoledronic acid 5mg IV single dose (following dental assessment)

EMETIC RISK

Day 1-3 High emetic risk (consider aprepitant and avoid dexamethasone)
Days 4-7 Moderate emetic risk
Day 8 Low emetic risk

INTERACTIONS

(Consult with pharmacist and refer for full details to individual medications SmPCs)

CYP3A4 inhibitors and inducers – consider potential for increased toxicity (with CYP3A4 inhibitors) and decreased efficacy (with CYP3A4 inducers) of doxorubicin, cyclophosphamide, etoposide, dacarbazine and vincristine

Antidiabetics – prednisolone may increase blood glucose levels. Patients with diabetes mellitus receiving concurrent insulin and/or oral hypoglycemic agents may require dosage adjustments.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

(Consult with pharmacist and refer to SPC for full details, also see DOSE MODIFACTIONS section)

Compared with ABVD, BEACOPDac is associated with more profound cytopenias, higher rates of febrile neutropenia, increased rates of infertility (although the purpose of replacing procarbazine with dacarbazine is to reduce this risk) and a roughly 2% risk of secondary MDS / AML.

Hypersensitivity reactions – highest risk with bleomycin and etoposide. Treatment is symptomatic. Photosensitivity reactions may occur rarely

Bleomycin is a component of this treatment and can cause pneumonitis – refer to Bleomycin supportive care document [Link].

EXTRAVASATION RISK

Bleomycin: neutral
Cyclophosphamide: neutral
Dacarbazine: -irritant
Doxorubicin: vesicant
Etoposide: irritant
Vincristine: vesicant

TREATMENT RELATED MORTALITY

1-2% (age-dependent)

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REVIEW

Name	Revision	Date	Version	Review date
Cheuk-kie Jackie Cheung (Haematology Pharmacist)	Amendment of dacarbazine diluent to 1000mL due to stability data, indication and restaging updated as per BEACOPP protocol review	July 2019	1.3	
Cheuk-kie Jackie Cheung (Haematology Pharmacist)	Deauville score in indication updated.	Sep 2019	1.4	May 2020
Catriona Gilmour Hamilton Lymphoid Quality Manager	Added Nursing Care Plan	June 2020	1.5	May 2022
NSSG Lymphoma Group	Annual protocol review	Aug 2020	1.6	May 2022
Graham Collins, Consultant Haematologist, Natalia Czub, Haematology Pharmacist, NSSG Lymphoma Group	Drug regimen, dose modifications, interactions, contraindications and references sections updated. Annual protocol review.	July 2022	2.0	July 2024

Nursing Care Plan: BEACOPDac-Escalated

Indication: Early Stage Classical Hodgkin Lymphoma with positive interim PET-CT. Advanced Classical Hodgkin Lymphoma.
Frequency:
BEACOPDac-Escalated every 21 days for 2-6 cycles
Alopecia: Yes
Emetic risk: High
Send a group and save sample to blood transfusion and inform patient and laboratory that they will require irradiated blood products for all future transfusions. Give patient an irradiated blood product booklet and card
B = BLEOMYCIN: Cytotoxic antibiotic
Administrated as IV infusion over 1 hour on day 8.
Classification of extravasation: neutral
Emetic risk : neutral
Side effects: fever, rigors, flu like symptoms, interstitial pneumonia, anorexia, nausea / vomiting, mucocitis, alopecia, nails deformation / discoloration, dizziness, diarrhoea, pulmonary fibrosis. Use with caution in patient with impaired respiratory function, ask patient to report any changes including SOB, cough or chest pain for the duration of chemotherapy.

E = ETOPOSIDE: Topoisomerase inhibitor
Administered as an infusion over 1 hour on days 1-3.
Classification of extravasation: irritant
Emetic risk: moderate.
Side effects: hypotension if infused in less than 30mins, anaphylaxis, arrhythmia, nausea and vomiting, anorexia, diarrhoea, fatigue, drowsiness, pneumonitis, bone marrow depression, alopecia, hepatic impairment.

A = DOXORUBICIN (Adriamycin): Anthracycline antibiotic
Administrated as IV bolus on day 1.
Classification of extravasation: vesicant
Emetic risk : moderate
Side effects : vein pain, red flush 'flare' reaction with higher doses/ sensitive veins, nausea/vomiting, red urine, mucositis, alopecia, Palmar Plantar Erythrodysaesthesia (PPE), bone morrow depression, fatigue, nail and skin pigmentation, life threatening cardiac toxicity/ cardiac symptoms.
C = CYCLOPHOSPHAMIDE: Alkylating agent.
Administered as IV bolus on day 1 (note on escalated protocol IV Mensa bolus is given with the Cyclophosphamide).
Classification of extravasation: neutral.
Emetic risk: high (when used in combination with doxorubicin).
Side effects: nasal stuffiness (can be reduced by slowing rate of administration), dizziness, nausea and vomiting, diarrhoea, anorexia, taste changes, bone marrow suppression, alopecia, risk of haemorrhagic cystitis in patients with pre-existing bladder conditions, infertility (most cases reversible), renal and hepatic impairment.

O = VINCRISTINE (Oncovin): Vinca Alkaloid.
Administered as 10 minute IV infusion on day 8.

Classification of extravasation: vesicant.
Emetic risk: low.
Side effects: cold sensation along vein, jaw pain, constipation, peripheral neuropathy, alopecia.

P = PREDNISOLONE: Steroid.
Administered orally (days 1-7, or 1-14 on escalated protocol).
Side effects: increased appetite, GI disturbance, mood swings, restlessness, insomnia, hyperglycaemia, increased susceptibility to infection.

D = DACARBAZINE : Alkylating agent
Administrated as 1 to 2 hour IV infusion on days 2-3.
Classification of extravasation : vesicant
Emetic risk : high
Side effects : arm ache/ vein pain (can be severe and occur up to 3 days post administration) when given via cannula (run with fast flowing 0.9% saline, use heat pad and give over 2 hours if dacarbazine is given peripherally), nausea/vomiting, anorexia, diarrhoea, headache, facial flushing, bone morrow depression, alopecia.

Regime Specific Considerations

- Bloods pre chemo on days 1 and 8. On the escalated protocol bloods need to be checked 1-2 times per week due to the high rate of cytopenias.
- Anticipatory nausea and vomiting can be an issue. Consider use of lorazepam night before and day of chemotherapy and/or aprepitant.
- Placement of PICC line is highly recommended due to vesicant nature of drugs and risk of arm pain which can be severe.
- GCSF starts on Day 4, ensure patient/carer are taught to self administer this. Arrange a district nursing referral and prescription if this is not possible.
- Mesna is routinely required for BEACOPDac-Escalated (not BEACOPDac-14).
- Advise patients that it is important to maintain fluid intake of at least 3 litres on days where Cyclophosphamide is given.
- When given peripherally, Vincristine must be administered via a gravity drip, never through a pump. The nurse must remain with the patient throughout the infusion in order to detect any signs of extravasation.