Brentuximab vedotin and cycloPHOSphamide, DOXOrubicin and prednisoLONE (CHP) Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE reimbursement status*
Brentuximab vedotin in combination with cycloPHOSphamide, DOXOrubicin and prednisoLONE (CHP) for use in adult patients with previously untreated systemic anaplastic large cell lymphoma (sALCL)	C84	00801	Brentuximab vedotin: ODMS 20/12/2022 cycloPHOSphamide and DOXOrubicin: 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 patients individual clinical circumstances.

Brentuximab vedotin and CHP are administered on Day 1 of each cycle every 21 days for up to 6 to 8 cycles.

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

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1-5	prednisoLONE	100mg*	PO		Every 21 days
2	1	DOXOrubicin[a]	50mg/m^2	IV Bolus	Into the side arm of a fast running 0.9% NaCl infusion	Every 21 days
3	1	cycloPHOSphamide	750mg/m^2	IV infusion[b]	250 mL 0.9% NaCl over 30 minutes	Every 21 days
4	1	Brentuximab vedotin[c]	1.8mg/kg[d] (max. dose 180mg)	IV infusion[e]	150mL 0.9% NaCl[f, g] over 30 minutes	Every 21 days
5	6 onwards	G-CSF[h]	5mcg/kg	SC (Round to nearest whole syringe)	Daily injection for 7 days or until ANC >1x10^9/L for 2 consecutive days	

*Alternative steroid regimens may be used at consultant discretion.

[a] 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.

[b] cycloPHOSphamide may also be administered as an IV bolus over 5-10 minutes.

[c] Brentuximab to be administered within one hour of completing treatment with other agents administered via IV infusion.

[d] For patient weight > 100kg, the dose calculation should use 100kg.

[e] Patient should be carefully monitored during and after infusion in case of infusion related reactions.

[f] Final concentration of brentuximab should be 0.4-1.2mg/mL

[g] Glucose 5% or Compound Sodium Lactate (Hartmann's Solution) may also be used as diluent.

[h] G-CSF support is recommended with this regimen **(Refer to local policy)**

Note: Administration volumes and fluids have been standardised to facilitate electronic prescribing system builds.

ELIGIBILITY:

- Indications as above
- Aged ≥ 18 years
- Confirmation of CD30 expression using a validated test method
- ECOG 0-2
- Adequate organ function

EXCLUSIONS:

- Known hypersensitivity to brentuximab vedotin, cycloPHOSphamide, DOXOrubicin, prednisoLONE or any of the excipients
- Patients with known cerebral / meningeal disease, including a history of progressive multifocal leukoencephalopathy (PML)
- LVEF <50% (MUGA or echocardiogram)
- A cumulative life-long dose of 450 mg/m^2 of DOXOrubicin should only be exceeded with extreme caution as there is as risk of irreversible congestive heart failure
- Pregnancy / breastfeeding

- Combined use of bleomycin and brentuximab vedotin is contraindicated due to pulmonary toxicity

PRESCRIPTIVE AUTHORITY:

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

TESTS:

Baseline tests:

- FBC, renal and liver profile
- Blood glucose
- Confirmation of CD30+ PTCL using a validated test method
- Assessment of pre-existing neuropathy
- ECG
- MUGA, ECHO (LVEF > 50% to administer DOXOrubicin) if >65 years or dynamic cardiac monitoring (e.g. BNP) as clinically indicated
- LDH, Uric acid
- Virology screen-Hepatitis B* (HBsAg, HBcoreAb), Hepatitis C, HIV
  *Hepatitis B reactivation: Regimen specific complications

Regular tests:

- FBC, renal and liver profile
- Blood glucose and LDH prior to each cycle
- Clinical assessment to exclude neuropathy
- MUGA, ECHO or / dynamic cardiac monitoring (e.g. BNP) as clinically indicated (DOXOrubicin)

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.
- Dose modifications for the management of brentuximab vedotin and chemotherapy induced toxicity are permitted as outlined in Tables 1, 2 and 3 below.

Haematological:

- If neutropenia develops during treatment, see Table 1 for appropriate dosing recommendations for combination therapy.

Table 1: Dosing recommendations for neutropenia during combination therapy

ANC ($x10^9$/L)	Modification of dosing schedule
<1.5	Primary prophylaxis with G-CSF, beginning with the first dose, is recommended for all adult patients receiving combination therapy **(Refer to local policy).** Continue with the same dose and schedule.

Renal and Hepatic Impairment:

- Patients with renal and hepatic impairment should be closely monitored for adverse effects during treatment with brentuximab vedotin

Table 2: Dose modification in renal and hepatic impairment

Drug	Renal Impairment		Hepatic impairment	
Brentuximab vedotin [a]	There is no clinical trial experience in patients with renal impairment, where CrCl is ≤40 mL/minute. Use of brentuximab vedotin in combination with chemotherapy should be avoided in patients with severe renal impairment- discuss with consultant.		Mild**:** The recommended starting dose is 1.2 mg/kg every 3 weeks. Moderate to Severe**:** There is no clinical trial experience, therefore this combination should be avoided- discuss with consultant.	
cycloPHOSphamide [b]	**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		
DOXOrubicin[c]	**CrCl (mL/min)**	**Dose**	**Total 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

[a] Brentuximab vedotin: renal and hepatic dose modifications from SmPC,
[b] cycloPHOSphamide: renal and hepatic dose modifications from Giraud et al, 2023,

[c] DOXOrubicin: renal and hepatic dose modifications from Giraud et al 2023.

Management of adverse events:

Table 3 Dosing recommendations for new or worsening peripheral sensory or motor neuropathy during combination therapy during combination therapy

Adverse reactions	Dose	
Peripheral sensory or motor neuropathy*	Grade 1	Continue with the same dose and schedule.
	Grade 2	Sensory neuropathy: Continue treatment at same dose level. Motor neuropathy: Reduce dose to 1.2 mg/kg, up to a maximum of 120 mg every 3 weeks.
	Grade 3	Sensory neuropathy: Reduce dose to 1.2 mg/kg up to a maximum of 120 mg every 3 weeks. Motor neuropathy: Discontinue treatment.
	Grade 4	Discontinue treatment.
Progressive Multifocal Leukoencephalopathy (PML)		Discontinue treatment.
Severe cutaneous adverse reactions (SCARs)		Discontinue treatment.
*Grading based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03		

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

- As outlined in NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting linked here:

Brentuximab vedotin: Low **(Refer to local policy).**
DOXOrubicin / cycloPHOSphamide High **(Refer to local policy)**

For information:
Within NCIS regimens, antiemetics have been standardised by Medical Oncologists and Haemato-oncologists and information is available in the following documents:

- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Medical Oncology) - link here
- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Haemato-oncology) - link here

PREMEDICATIONS:

- Patients who have experienced a prior infusion-related reaction with brentuximab vedotin should be pre-medicated with analgesics, antihistamines and corticosteroids for subsequent infusions.

OTHER SUPPORTIVE CARE:

- Patients receiving brentuximab vedotin who are eligible for allogeneic transplantation should receive irradiated blood products.
- Proton pump inhibitor **(Refer to local policy).**
- Tumour Lysis Syndrome prophylaxis **(Refer to local policy).**
- PJP prophylaxis **(Refer to local policy).**
- Anti-fungal prophylaxis **(Refer to local policy).**
- Anti-viral prophylaxis **(Refer to local policy).**
- Patients should have an increased fluid intake of 2-3 litres on day 1 and day 2 to prevent haemorrhagic cystitis associated with cycloPHOSphamide.

ADVERSE EFFECTS

Please refer to the relevant Summary of Product Characteristics (SmPC) for full details.

REGIMEN SPECIFIC COMPLICATIONS:

Hepatitis B Reactivation: 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.

DRUG INTERACTIONS:

Current SmPC and drug interaction databases should be consulted for information.

REFERENCES:

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2. Horwitz S et al. The ECHELON-2 Trial: 5-year results of a randomized, phase 3 study of brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma. Ann Oncol. 2021 Dec 15:S0923-7534(21)04875-4. doi: 10.1016/j.annonc.2021.12.002. Epub ahead of print. PMID: 34921960.
3. 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/
4. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V5 2023. Available at:

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5. Brentuximab (Adcetris®) Summary of Product Characteristics. Last updated: 01/12/2023. Accessed 08/04/2024. Available at: https://www.ema.europa.eu/en/documents/product-information/adcetris-epar-product-information_en.pdf
6. cycloPHOSphamide (Endoxana®) Summary of Product Characteristics. Last updated: 02/08/2023 . Accessed: 11/04/2024. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2299-027-002_21122018112109.pdf
7. DOXOrubicin 2mg/mL Solution of Infusion Summary of Product Characteristics. Last updated: 20/02/2024. Accessed 11/04/2024. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2315-083-001_20022024123027.pdf

Version	Date	Amendment	Approved By
1	20/12/2022		Dr Amjad Hayat
2	22/08/2024	Reviewed. Added G-CSF to the treatment table. Updated exclusions section. Updated baseline and regular tests section. Updated Table 2 renal and hepatic dose recommendations. Updated Table 3 to align with SmPC. Updated emetogenic potential. Updated in line with NCCP standardisation.	Dr. Amjad Hayat

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