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

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	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: 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.

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

G-CSF support (using standard or pegylated form) is required with all cycles.

Facilities to treat anaphylaxis MUST be present when the chemotherapy is administered.

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1-5	prednisoLONE	100mg*	PO		Every 21 days
2	1	DOXOrubicin[1]	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[2]	250 ml 0.9% NaCl over 30 minutes	Every 21 days
4	1	Brentuximab vedotin[3]	1.8mg/kg[4] (max. dose 180mg)	IV infusion[5]	150ml 0.9% NaCl[6] over 30 minutes	Every 21 days
*Alternative steroid regimens may be used at consultant discretion.						
[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 outlined below[i] and to the age of the patient.						
[2] Cyclophosphamide may also be administered as an IV bolus over 5-10mins.						
[3] Brentuximab to be administered within one hour of completing treatment with other agents administered via IV infusion.						
[4] For patient weight > 100kg, the dose calculation should use 100kg. Final concentration of brentuximab should be 0.4-1.2mg/ml						
[5] Patient should be carefully monitored during and after infusion in case of infusion related reactions.						
[6] Dextrose 5% or Lactated Ringer's for Injection may also be used as diluent.						

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).
- 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 Medical Oncologist or by a Consultant 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 or ECHO should be considered prior to the administration of DOXOrubicin
- LDH, Uric acid
- Virology screen-Hepatitis B (HBsAg, HBcoreAb), Hepatitis C, HIV
  *Hepatitis B reactivation: See adverse events/ Regimen specific complications

Regular tests:

- FBC, renal and liver profile
- Blood glucose and LDH prior to each cycle
- Clinical assessment to exclude neuropathy
- MUGA or ECHO as 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.
- 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

<table>
<tr><th>Drug</th><th colspan="2">Renal Impairment</th><th colspan="2">Hepatic impairment</th></tr>
<tr><td>Brentuximab vedotin</td><td colspan="2">There is no clinical trial experience using brentuximab vedotin in combination with chemotherapy in patients with renal impairment, where CrCl is ≤40 mL/min. Use of brentuximab vedotin in combination with chemotherapy should be avoided in patients with severe renal impairment.</td><td colspan="2">The recommended starting dose in patients with mild hepatic impairment receiving brentuximab vedotin in combination with CHP is 1.2 mg/kg. There is no clinical trial experience using brentuximab vedotin in combination with chemotherapy in patients with moderate to severe, therefore this combination should be avoided in patients with moderate and severe hepatic impairment.</td></tr>
<tr><td rowspan="4">Cyclophosphamide</td><td>CrCl (ml/min)</td><td>Dose</td><td colspan="2" rowspan="4">Severe impairment. Clinical Decision.</td></tr>
<tr><td>>20</td><td>100%</td></tr>
<tr><td>10-20</td><td>75%</td></tr>
<tr><td><10</td><td>50%</td></tr>
<tr><td rowspan="5">DOXOrubicin</td><td colspan="2" rowspan="5">No dose reduction required.
Clinical decision in severe impairment.</td><td>Serum Bilirubin (micromol/L)</td><td>Dose</td></tr>
<tr><td>20-50</td><td>50%</td></tr>
<tr><td>51-85</td><td>25%</td></tr>
<tr><td>>85</td><td>Omit</td></tr>
<tr><td colspan="2">If AST 2-3 x normal, give 75%.
If AST > 3 x ULN, give 50%.</td></tr>
</table>

Management of adverse events:

Table 3: Dose modification of brentuximab vedotin based on adverse events

Adverse reactions*	Recommended dose modification
Sensory neuropathy • Grade 2 • Grade 3 • Grade 4	 Continue treatment at same dose level Reduce dose to 1.2 mg/kg up to a maximum of 120 mg every 3 weeks. Discontinue
Motor neuropathy • Grade 2 • Grade ≥3	 Reduce dose to 1.2 mg/kg up to a maximum of 120 mg every 3 weeks Discontinue
PML**	Discontinue
Severe cutaneous adverse reactions (SCARs)	Discontinue

*Grading based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03; see neuropathy: motor; neuropathy: sensory; and neuropathic pain.
**PML = Progressive multifocal leukoencephalopathy

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

Brentuximab vedotin: Low **(Refer to local policy).**
Cyclophosphamide: Moderate **(Refer to local policy).**
DOXOrubicin: Moderate **(Refer to local policy).**

PREMEDICATIONS:

- Patients who have experienced a prior infusion-related reaction with brentuximab 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 / 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**: 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.

Brentuximab:

- **Progressive multifocal leukoencephalopathy (PML):** John Cunningham virus (JCV) reactivation resulting in PML and death can occur in brentuximab vedotin-treated patients. Patients should be closely monitored for new or worsening neurological, cognitive, or behavioural signs or symptoms which may be suggestive of PML. Brentuximab vedotin dosing should be held for any suspected case of PML. If a diagnosis of PML is confirmed, treatment with brentuximab vedotin should be permanently discontinued.
- **Pancreatitis:** Acute pancreatitis has been observed in patients treated with brentuximab vedotin. Fatal outcomes have been reported. Patients should be closely monitored for new or worsening abdominal pain, which may be suggestive of acute pancreatitis. Brentuximab vedotin should be held for any suspected case of acute pancreatitis. Brentuximab vedotin should be discontinued if a diagnosis of acute pancreatitis is confirmed.
- **Pulmonary Toxicity:** Cases of pulmonary toxicity, including pneumonitis, interstitial lung disease, and acute respiratory distress syndrome (ARDS), some with fatal outcomes, have been reported in patients receiving brentuximab vedotin. Although a causal association with brentuximab vedotin has not been established, the risk of pulmonary toxicity cannot be ruled out. In the event of new or worsening pulmonary symptoms (e.g. cough, dyspnoea), a prompt diagnostic evaluation should be performed and patients should be treated appropriately. Consider holding brentuximab vedotin dosing during evaluation and until symptomatic improvement.
- **Serious infections and opportunistic infections**: Patients should be carefully monitored during treatment for the emergence of possible serious and opportunistic infections.
- **Infusion-related reactions**: Immediate and delayed infusion-related reactions (IRR), as well as anaphylactic reactions, have been reported. Patients should be carefully monitored during and after infusion. If an anaphylactic reaction occurs, administration of brentuximab vedotin should be immediately and permanently discontinued and appropriate medical therapy should be administered. If an IRR occurs, the infusion should be interrupted and appropriate medical management instituted. The infusion may be restarted at a slower rate after symptom resolution.
- **Tumour lysis syndrome**: Patients with rapidly proliferating tumour and high tumour burden are at risk of tumour lysis syndrome. These patients should be monitored closely and managed according to best medical practice.
- **Peripheral neuropathy**: Brentuximab vedotin treatment may cause a peripheral neuropathy, both sensory and motor. Brentuximab vedotin-induced peripheral neuropathy is typically an effect of cumulative exposure to this medicinal product and is reversible in most cases. Patients

experiencing new or worsening peripheral neuropathy may require a delay and a dose reduction of brentuximab vedotin or discontinuation of treatment.

- **Severe cutaneous adverse reactions (SCARs)**: Cases of SCARs, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported with brentuximab vedotin. Fatal outcomes have been reported for SJS and TEN. If SJS, TEN or DRESS occur, brentuximab vedotin should be discontinued and appropriate medical therapy should be administered.
- **Gastrointestinal Complications**: Gastrointestinal (GI) complications including intestinal obstruction, ileus, enterocolitis, neutropenic colitis, erosion, ulcer, perforation and haemorrhage, some with fatal outcomes, have been reported in patients treated with brentuximab vedotin. In the event of new or worsening GI symptoms, perform a prompt diagnostic evaluation and treat appropriately.
- **Hyperglycaemia**: Hyperglycaemia has been reported during clinical trials in patients with an elevated Body Mass Index (BMI) with or without a history of diabetes mellitus. Any patient who experiences hyperglycaemia should have their serum glucose closely monitored. Anti-diabetic treatment should be administered as appropriate.
- **Sodium content in excipients**: This medicinal product contains a maximum of 2.1mmol of sodium per dose, which needs to be taken into consideration for patients on a controlled sodium diet.

DOXOrubicin:

- **Extravasation**: DOXOrubicin may cause pain and tissue necrosis if extravasated. (Refer to local extravasation guidelines).
- **Cardiac Toxicity**: DOXOrubicin is cardiotoxic and must be used with caution, if at all, in patients with severe hypertension or cardiac dysfunction.

DRUG INTERACTIONS:

- DOXOrubicin cardiotoxicity is enhanced by previous or concurrent use of other anthracyclines, or other potentially cardiotoxic drugs (e.g. 5-FU, cyclophosphamide or PACLitaxel) or with products affecting cardiac function (e.g. calcium antagonists).
- Current drug interaction databases should be consulted for more information including potential for interactions with CYP3A4 inhibitors/inducers.
- Current drug interaction databases should be consulted for more information.

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Version	Date	Amendment	Approved By
1	20/12/2022		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