BC Cancer Protocol Summary for Treatment of CD30-Positive Peripheral T-Cell Lymphoma (PTCL) with DOXOrubicin, Cyclophosphamide, predniSONE (CHP) and Brentuximab Vedotin

Protocol Code	*LYCHPBV*
Tumour Group	*Lymphoma*
Contact Physicians	*Dr. Laurie Sehn*
	Dr. Kerry Savage

ELIGIBILITY:

- Patients must have one of the following previously untreated adult CD30 positive tumours:
  - Systemic anaplastic large-cell lymphoma (ALCL),
  - Peripheral T-cell lymphoma not otherwise specified (PTCL-NOS), or
  - Angioimmunoblastic T-cell lymphoma.

EXCLUSIONS:

- Other PTCL subtypes

CAUTION:

- Congestive cardiac failure requiring current treatment (LYCHPBV may be used but DOXOrubicin should be omitted, see cardiotoxicity below)

TESTS:

- Baseline (required before first treatment): CBC and diff, platelets, bilirubin, ALT, creatinine
- Baseline (required, but results do not have to be available to proceed with first treatment**;** results must be checked before proceeding with cycle 2): LDH, HBsAg, HBcoreAb
- Before day 1 of each treatment: CBC and diff, platelets, (and bilirubin if elevated at baseline)
- If clinically indicated: creatinine, ALT, bilirubin, LDH

PREMEDICATIONS:

- Antiemetic protocol for highly emetogenic chemotherapy (see protocol SCNAUSEA)
- If past brentuximab vedotin drug reactions:
  - diphenhydramine 50 mg PO 30 minutes prior to brentuximab vedotin
  - acetaminophen 650 mg to 975 mg PO 30 minutes prior to brentuximab vedotin

SUPPORTIVE MEDICATIONS:

If HBsAg or HBcoreAb positive, start lamiVUDine 100 mg PO daily for the duration of chemotherapy and continue for one year from treatment completion for patients who are HBsAg positive and for six months for patients who are HBcoreAb positive.

TREATMENT:

Filgrastim is mandatory for primary prevention of neutropenia. Submit a special authority request to Pharmacare for filgrastim coverage.

Drug	Dose	BC Cancer Administration Guideline
DOXOrubicin	50 mg/m^2 on day 1	IV push
cyclophosphamide	750 mg/m^2 on day 1	IV in 100 to 250* mL NS over 20 min to 1 hour (*use 250 mL for doses greater than 1000 mg)
predniSONE	45mg/m2 on days 1 to 5	PO in the morning with food
Brentuximab* vedotin	1.8 mg/kg on Day 1	IV in 100 mL NS over 30 minutes
filgrastim	5 mcg/kg daily x 5 days starting on day 7 300 mcg: up to 75 kg 480 mcg: 76 kg to 110 kg 600 mcg: greater than 110 kg	SC

*The dose for patients weighing greater than 100 kg should be calculated based on a weight of 100 kg.

Repeat every 21 days for 6 cycles

DOSE MODIFICATIONS:

1. **Elderly Patients (age greater than 75 years)**:

Cycle 1 doses of cyclophosphamide and DOXOrubicin should be administered at 75% doses. Further treatment should be given at the maximum dose tolerated by the patient, trying to escalate up to full 100% doses, but using the baseline experience with the 75% doses to guide these decisions.

Hematological:
All drugs:

ANC ($x10^9$/L)	Dose Modification
greater than or equal to 0.8	100%
less than 0.8	Delay until recovery

Consider RBC transfusion support in individuals that have an expected hemoglobin nadir below 70 to 80 g/L and platelet transfusions to keep platelets greater than 20 x 10^9/L.

2. **Peripheral Neuropathy:**

Toxicity	brentuximab vedotin dose
Grade 1	100%
Grade 2 or 3	Hold until neuropathy improves to grade 1 or baseline, then decrease dose to 1.2 mg/kg
Grade 4	Discontinue

2. **Hepatotoxicity**: DOXOrubicin only:

Bilirubin (micromol/L)	Dose Modification
2 to 35	100%
35 to 85	50%
Greater than 85	Omit DOXOrubicin. ***ADD*** cyclophosphamide 350 mg/m^2 to the dose already planned.

Note: This adjustment is only necessary for the initial treatment. After the hyperbilirubinemia has resolved, adjustment is only necessary if overt jaundice re-occurs. Serum bilirubin does not need to be requested before each treatment.

3. **Cardiotoxicity**: DOXOrubicin only:
When DOXOrubicin cannot be used due to proven cardiac dysfunction, it can be replaced by etoposide 50 mg/m^2 IV on day 1, 100 mg/m^2 PO on day 2 and 3. (Use non-DEHP equipment with in-line filter)

PRECAUTIONS:
1. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively.
2. **Thrombocytopenia**: Support with platelet transfusion may be required.
3. **Cardiac Toxicity**: DOXOrubicin is cardiotoxic and must be used with caution, if at all, in patients with severe hypertension or cardiac dysfunction. Cardiac assessment is recommended if patient has received greater than or equal to 300 mg/m^2 of doxorubicin. (BC Cancer Cancer Drug Manual). Work-up may include an assessment of cardiac ejection fraction, and cardiac oncology referral if necessary
4. **Extravasation**: DOXOrubicin causes pain and tissue necrosis if extravasated. Brentuximab vedotin causes pain and may, rarely, cause tissue necrosis if extravasated. Refer to BC Cancer Extravasation Guidelines.
5. **Infusion-related reactions**: If applicable, monitor etoposide infusion for the first 15 minutes for signs of hypotension. Infusion-related reactions, including anaphylaxis, have occurred with brentuximab vedotin. Monitor patients during infusion of brentuximab vedotin. If an infusion reaction occurs, stop the infusion. Refer to BC Cancer Infusion-Related Reactions Guidelines.
6. **Peripheral neuropathy:** Brentuximab vedotin causes cumulative peripheral sensory neuropathy and sometimes peripheral motor neuropathy. Monitor patients for symptoms of neuropathy, such as hypoesthesia, hyperesthesia, paresthesia, discomfort, a burning sensation, neuropathic pain or weakness, and institute dose modifications accordingly.
7. **Hepatitis B Reactivation**: All lymphoma patients should be tested for both HBsAg and HBcoreAb. If either test is positive, such patients should be treated with lamiVUDine during chemotherapy and continue for one year from treatment completion for patients who are HBsAg positive and for six months for patients who are HBcoreAb positive. Such patients should also be monitored with frequent liver function tests and hepatitis B virus DNA at least every two months. If the hepatitis B virus DNA level rises during this monitoring, management should be reviewed with an appropriate specialist with experience managing hepatitis and consideration given to halting chemotherapy.
8. **Tumor lysis syndrome:** Patients with rapidly proliferating tumour and high tumour burden are at risk of tumour lysis syndrome from brentuximab vedotin and should be monitored closely.
9. **Progressive multifocal leukoencephalopathy (PML):** JC virus infection resulting in PML and death has been reported with brentuximab vedotin. Consider the diagnosis of PML in any patient presenting with new onset signs and symptoms of central nervous system abnormalities. Hold brentuximab vedotin if PML is suspected.
10. **Stevens-Johnson syndrome:** Stevens-Johnson syndrome has been reported with brentuximab vedotin. If it occurs, discontinue brentuximab vedotin,
11. **Acute pancreatitis** including fatal outcomes, has been reported in patients who have received brentuximab vedotin. Consider the diagnosis of acute pancreatitis for patients who present with new or worsening abdominal pain. Hold brentuximab vedotin if suspected pancreatitis and discontinue if confirmed.

Call Dr. Laurie Sehn, Dr. Kerry Savage or tumour group delegate at (604) 877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.

References:

1. Horwitz S, O'Connor OA, Pro B. et al. Brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma (ECHELON-2):a randomized, double-blind, phase 3 trial. Lancet 2019; 393 (10168):229-240.
2. Seattle Genetics Inc. ADCETRIS® product monograph. Bothell, Washington; June 2018.