BC Cancer Protocol Summary for Treatment of Previously Untreated, Stage IV Hodgkin Lymphoma with DOXOrubicin, vinBLAStine, Dacarbazine and Brentuximab Vedotin

***Protocol Code**:* *LYAVDBV*

***Tumour Group**:* *Lymphoma*

***Contact Physicians**:* *Dr. Laurie Sehn, Dr. Kerry Savage*

Contact Pharmacist: *Louisa Pang*

ELIGIBILITY:

Patients should have:
- Previously untreated, stage IV classical Hodgkin lymphoma

Note:
- Patients on active treatment responding to LYABVD may be eligible to switch to LYAVDBV

EXCLUSIONS:
- Use with caution in patients greater than 60 years of age
- Nodular lymphocyte-predominant Hodgkin lymphoma
- Pre-existing peripheral sensory or motor neuropathy of grade 2 or more
- Cerebral or meningeal disease, including signs or symptoms of progressive multifocal leukoencephalopathy

TESTS:
- Baseline (required before first treatment): CBC & 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): HBsAg, HBcoreAb
- Before day 1 of each cycle: CBC & diff, platelets, (and bilirubin if elevated at baseline). Note: No tests are required before day 15.

PREMEDICATIONS:
- Antiemetic protocol for highly emetogenic chemotherapy (see protocol SCNAUSEA)
- If past brentuximab vedotin drug reactions:
  - diphenhydrAMINE 50mg PO 30 minutes prior to brentuximab vedotin
  - acetaminophen 650-975 mg PO 30 minutes prior to brentuximab vedotin
- If past etoposide drug reactions:
  - hydrocortisone 100 mg IV prior to etoposide
  - diphenhydrAMINE 50 mg IV prior to etoposide

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.

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

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
DOXOrubicin	25 mg/m^2 on days 1 and 15	IV push
vinBLAStine	6 mg/m^2 on days 1 and 15	IV in 50 mL NS over 15 minutes
dacarbazine	375 mg/m^2 on days 1 and 15	IV in 250 to 500 mL NS or D5W over 1 to 2 hours
brentuximab vedotin*	1.2 mg/kg on days 1 and 15	IV in 50 to 100 mL NS over 30 minutes
filgrastim	5 mcg/kg daily x 5 days starting on day 7 and day 21 300 mcg: up to 75 kg 480 mcg: 76 kg to 110 kg 600 mcg: greater than 110 kg	Subcutaneous

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

Repeat every 28 days x 6 cycles

PET scan after Cycle 2 to assess response to treatment.

Obtain end-of-treatment CT and PET

- If CR after 6 cycles, no further treatment.
- If PET positive after 6 cycles and without evidence of progression → consider consolidative radiation to PET positive site if feasible
- If PET positive after 6 cycles and without evidence of progression, but radiation is not feasible → consider close observation or biopsy to direct further treatment on proof of persistent lymphoma

DOSE MODIFICATIONS:

1. **Hematological**:

ANC (x 10^9/L)	Dose Modification
greater than or equal to 0.6	100 %
less than 0.6	Consider delaying treatment for 1 week until ANC greater than 0.6 x 10^9/L. If necessary, consider dose reduction of brentuximab vedotin to 0.9 mg/kg followed by further dose reduction as necessary.

Transfuse as needed to keep hemoglobin greater than 90 g/L, platelets greater than 20 x 10^9/L

2. **Peripheral Neuropathy**:

Only one component of chemotherapy should be modified at a time for peripheral neuropathy (PN).

- The first modification should be reducing brentuximab vedotin to 0.9 mg/kg for grade 2 PN.
- If grade 3 PN does not improve after brentuximab vedotin has been discontinued, vinBLAStine dose may be dose reduced or discontinued.
- If PN improves to grade 2 or better after above steps, vinblastine may be resumed followed by brentuximab vedotin in a stepwise fashion

For brentuximab vedotin

Toxicity	Dose Modification
Grade 1	100%
Grade 2	Decrease dose to 0.9 mg/kg
Grade 3	Hold until toxicity resolves to less than or equal to grade 2, then reduce dose to 0.9 mg/kg and resume treatment. If already at 0.9 mg/kg, discontinue
Grade 4	Discontinue

For vinBLAStine

Toxicity	Dose Modification
Dysesthesias, areflexia only	100%
Abnormal buttoning, writing	67%
Motor neuropathy, moderate	50%
Motor neuropathy, severe	Omit

3. **Hepatotoxicity**: For DOXOrubicin

Bilirubin (micromol/L)	Dose Modification
2 to 35	100%
35 to 85	50%
greater than 85	Omit DOXOrubicin. Substitute cyclophosphamide 375 mg/m^2

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.

Hepatotoxicity: For vinBLAStine

Bilirubin (micromol/L)	Dose Modification
Less than 25	100%
25 to 50	50%
Greater than 50	25%

4. **Cardiotoxicity**: DOXOrubicin only
   When DOXOrubicin cannot be used due to proven cardiac dysfunction, each dose of DOXOrubicin can be replaced by etoposide 25 mg/m^2 IV on the first day (Use non-DEHP equipment with in-line filter), 50 mg/m^2 PO on the second and third days
5. **Dacarbazine unavailability**: Occasionally dacarbazine becomes unavailable due to manufacturing or other problems. If this occurs**,** and only if dacarbazine is completely unavailable, the Lymphoma Tumour Group recommends that Compassionate Access Program (CAP) approval be sought for cyclophosphamide 375 mg/m^2 to be substituted for each dose of the dacarbazine until the supply is renewed. There are no direct data that this substitution is equally effective, however, cyclophosphamide is an effective drug for Hodgkin lymphoma, works via the same class of mechanisms (alkylation), causes the same minimal level of myelosuppression at this dose and is not sterilizing for men or women at this dose. When used at this dose no adjustment for myelosuppression is required.

PRECAUTIONS:

1. **Neutropenia**: fever or other evidence of infection must be assessed promptly and treated aggressively.
2. **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 Drug Manual). Work-up may include an assessment of cardiac ejection fraction, and cardiac oncology referral if necessary.
3. **Extravasation**: DOXOrubicin and vinBLAStine cause pain and tissue necrosis if extravasated. Refer to BC Cancer Extravasation Guidelines.
4. **Infusion-Related Reactions**: Infusion-related reactions, including anaphylaxis, have occurred with brentuximab vedotin. Monitor patients during infusion. If an infusion reaction occurs refer to BC Cancer Hypersensitivity Guidelines. If applicable, monitor brentuximab vedotin infusion for the first 15 minutes for signs of hypotension. Refer to BC Cancer Infusion-Related Reactions Guidelines
5. **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.
6. **Peripheral neuropathy:** Brentuximab vedotin and vinBLAStine cause peripheral sensory neuropathy. Cases of peripheral motor neuropathy have also been reported. VinBLAStine can also cause autonomic 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. **Tumor lysis syndrome:** Patients with rapidly proliferating tumor and high tumor burden are at risk of tumor lysis syndrome and these patients should be monitored closely.
8. **Progressive multifocal leukoencephalopathy (PML):** JC virus infection resulting in PML and death has been reported in brentuximab vedotin-treated patients. 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.

9. **Stevens-Johnson syndrome:** Stevens-Johnson syndrome has been reported with brentuximab vedotin. If Stevens-Johnson syndrome occurs, discontinue brentuximab vedotin.
10. **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. Connors JM et al. Brentuximab vedotin with chemotherapy for stage III or IV Hodgkin's lymphoma. N Engl J Med 2018;378(4):331-344.
2. Younes A et al. Brentuximab vedotin combined with ABVD or AVD for patients with newly diagnosed Hodgkin's lymphoma: a phase 1, open-label, dose-escalation study. Lancet Oncol 2013;14(13):1348-56.
3. Straus D et al. Brentuximab vedotin with chemotherapy for stage III/IV classical Hodgkin lymphoma: 3 year update of the ECHELON-1 study. Blood 2020;135(10):735-742.