BC Cancer Protocol Summary for Treatment of Previously Untreated, Stage IV Hodgkin Lymphoma with Sequential Brentuximab Vedotin and DOXOrubicin, vinBLAStine and Dacarbazine in Patients 60 Years or Older

***Protocol Code**:*	*LYBVAVDBV*
***Tumour Group**:*	*Lymphoma*
***Contact Physicians**:*	*Dr. Kerry Savage*

ELIGIBILITY:

Patients must:

- Have previously untreated, stage IV classical Hodgkin lymphoma,
- Not deemed suitable for LYAVDBV by the treating medical oncologist, and
- Be 60 years of age or older

Note: All other cases including patients less than 60 years not suitable for LYAVDBV require approval via BC Cancer Compassionate Access Program (CAP)

EXCLUSIONS:

Patients must not have:

- Nodular lymphocyte-predominant Hodgkin lymphoma
- Cerebral or meningeal disease, including signs or symptoms of progressive multifocal leukoencephalopathy

CAUTIONS:

- Pre-existing peripheral sensory or motor neuropathy of Grade 2 or more

TESTS:

- Baseline (required before first treatment): CBC & Diff, platelets, total 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, HBsAb, HBcoreAb
- Cycles 1 and 2 and Cycles 9 to 12 (brentuximab vedotin):
  - CBC & Diff, platelets prior to each cycle
  - If clinically indicated: creatinine, total bilirubin, ALT
- Cycles 3 to 8 (DOXOrubicin, vinBLAStine, and dacarbazine):
  - CBC & Diff, platelets prior to each cycle. Note: No tests are required before Day 15.
  - If clinically indicated: creatinine, total bilirubin, ALT

PREMEDICATIONS:

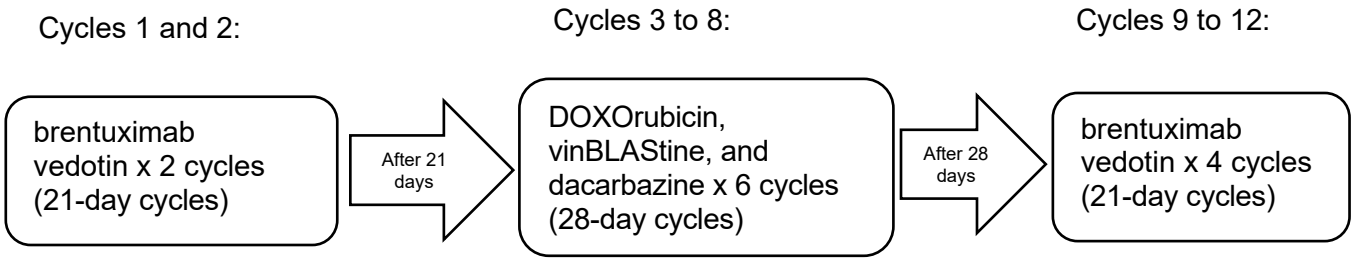
- For cycles of brentuximab vedotin, no routine antiemetics necessary
- If past brentuximab vedotin drug reactions:
  - diphenhydrAMINE 50 mg PO/IV 30 minutes prior to brentuximab vedotin
  - acetaminophen 650 to 975 mg PO 30 minutes prior to brentuximab vedotin

- For cycles of DOXOrubicin, vinBLAStine, and dacarbazine, antiemetic protocol for highly emetogenic chemotherapy (see protocol SCNAUSEA)
- If past etoposide drug reactions:
  - hydrocortisone 100 mg IV prior to etoposide
  - diphenhydrAMINE 50 mg IV prior to etoposide

SUPPORTIVE MEDICATIONS:

- High risk of hepatitis B reactivation. If HBsAg or HBcoreAb positive, start hepatitis B prophylaxis as per BC Cancer Protocol Summary for Hepatitis B Virus Reactivation (SCHBV).
- **Filgrastim is mandatory for primary prevention of neutropenia** for cycles containing DOXOrubicin, vinBLAStine, and dacarbazine. Submit a special authority request to Pharmacare for filgrastim coverage.

Treatment Schema:



TREATMENT:

- Cycles 1 and 2 **every 21 days**:

Drug	Dose	BC Cancer Administration Guideline
brentuximab vedotin*	1.8 mg/kg on Day 1	IV in 100 mL NS over 30 minutes

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

THEN

- Cycles 3 to 8 every **28 days** (*Cycle 3 to start 21 days after cycle 2*):

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
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	Subcutaneously

THEN

- Cycles 9 to 12 **every 21 days** *(Cycle 9 to start 28 days after cycle 8)*:

Drug	Dose	BC Cancer Administration Guideline
brentuximab vedotin*	1.8 mg/kg on Day 1	IV in 100 mL NS over 30 minutes

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

- PET recommended for staging and at end of treatment
- CT or PET scan after 3rd cycle of DOXOrubicin, vinBLAStine, and dacarbazine (i.e., after Cycle 5) to assess response to treatment

DOSE MODIFICATIONS:

1. **Hematological:** for brentuximab vedotin

ANC (x10^9/L)		Platelets (x10^9/L)	Brentuximab vedotin
Greater than or equal to 0.6	and	Greater than or equal to 50	100%
Less than 0.6	or	Less than 50	Delay until recovery

Hematological: for DOXOrubicin, vinBLAStine, and dacarbazine

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 Day 15 treatment is delayed, Day 1 of subsequent cycle should also be delayed to maintain treatment cadence

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:** for brentuximab vedotin

Toxicity	Dose Modification
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 brentuximab vedotin

Peripheral Neuropathy: 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

Total bilirubin (micromol/L)	Dose Modification
2 to 35	100%
36 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

Total 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. Brentuximab vedotin causes pain and may, rarely, cause 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 Management of Infusion-Related Reactions to Systemic Therapy Agents, SCDRUGRX. If applicable, monitor brentuximab vedotin infusion for the first 15 minutes for signs of hypotension.
5. **Hepatitis B Reactivation**: See SCHBV protocol for more details.
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. 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. Evens AM, Sweetenham JW, Horning SJ. Hodgkin lymphoma in older patients: an uncommon disease in need of study. Oncology (Williston Park). 2008 Nov 15;22(12):1369-79.
2. Evens AM, Advani RH, Helenowski IB, et al. Multicenter Phase II Study of Sequential Brentuximab Vedotin and Doxorubicin, Vinblastine, and Dacarbazine Chemotherapy for Older Patients With Untreated Classical Hodgkin Lymphoma. J Clin Oncol. 2018 Oct 20;36(30):3015-3022.