BC Cancer Protocol Summary for Treatment of Hodgkin Lymphoma with DOXOrubicin, Bleomycin, vinBLAStine, and Dacarbazine

***Protocol Code**:* *LYABVD*

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

***Contact Physician**:* *Dr. Laurie Sehn*

ELIGIBILITY:
- Histology: Hodgkin lymphoma, all stages

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, HBcoreAb, HBsAb
- Before day 1 of each cycle: CBC & Diff, platelets
- If clinically indicated, before day 1 of each cycle: total bilirubin, ALT, creatinine
- If clinically indicated: HBV viral load, HBsAg (see protocol SCHBV)
- Note: No tests are required before day 15.
- After cycle #2 (for all patients): PET Scan (ideally performed between day 21 and day 28 of cycle 2)

PREMEDICATIONS:
- Antiemetic protocol for highly emetogenic chemotherapy (see protocol SCNAUSEA)
- hydrocortisone 100 mg IV in 50 to 100 mL NS over 15 to 30 minutes prior to bleomycin on days 1 and 15
- 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).

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
bleomycin*	10 units/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 500 mL NS or D5W over 1 to 2 hours

Repeat each treatment cycle every 28 days.

*Discontinue bleomycin after cycle 2 if PET negative on interim PET done after cycle 2. See below for definition of PET negative, which varies according to stage:

PET-based Management According to Stage

(please note definition of PET negative varies according to stage, definitions below)

Limited Stage: ABVD x 2 cycles then PET scan

- **If PET negative** (Deauville score 1, 2) →AVD x 2 more cycles, omit bleomycin from cycles 3 and 4.
- **If PET positive** (Deauville score 3, 4, 5) without evidence of progression → no further chemotherapy, proceed to involved site radiation.
  - Obtain end-of-treatment CT.

Advanced Stage: ABVD x 2 cycles then PET scan

- **If PET negative** (Deauville score 1, 2, 3) → AVD x 4 cycles, omit bleomycin from cycles 3 to 6.
  - Obtain end-of-treatment CT and PET
- **If PET positive (Deauville score 4, 5) without evidence of progression → ABVD x 4 more cycles.**
  - CT scan after 4 cycles to rule out progression. Obtain both CT and PET at end-of-treatment.
  - 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	100 % plus filgrastim 5 mcg/kg* SC daily x 5 days starting on day 7 and day 21

The patient should be treated with Filgrastim (G-CSF) in doses sufficient to allow full dose treatment on schedule using the above dose modifications. Note: this guideline applies only if the treatment is potentially curative and after experience with one or more cycles of treatment indicate Filgrastim (G-CSF) is required. (See Pharmacare guidelines)

*Filgrastim 300 mcg: up to 75 kg

480 mcg: 76 kg to 110 kg

600 mcg: greater than 110 kg

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

2. **Neurotoxicity**: vinBLAStine only

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%
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

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

4. **Cardiotoxicity**: DOXOrubicin only
   DOXOrubicin is cardiotoxic and must be used with caution, if at all, in patients with severe hypertension or cardiac dysfunction. 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 bag and tubing with 0.2 micron in-line filter), 50 mg/m^2 PO on the second and third days. Cardiac assessment is recommended if patient has received greater than or equal to 300 mg/m2 of DOXOrubicin (BC Cancer Drug Manual). Work-up may include an assessment of cardiac ejection fraction, and cardiac oncology referral if necessary. NOTE: When doxorubicin is replaced with etoposide, administer etoposide IV in place of doxorubicin (follow same sequence).
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's 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. **Bleomycin**: may cause severe and life threatening pulmonary toxicity. Limiting the total dose to 270 units should decrease the risk but clinical assessment before each cycle must include a careful survey of respiratory symptoms, chest auscultation, and chest radiograph for pulmonary toxicity. Pulmonary function tests should be repeated in suspect cases. Febrile reaction can be prevented by hydrocortisone premedication. Oxygen may precipitate or aggravate bleomycin pulmonary toxicity. The FI O_2 must not exceed 30-40% unless absolutely necessary. The anesthesiologist must be aware of the bleomycin history before any surgery: an alert bracelet is recommended.
2. **Neutropenia**: fever or other evidence of infection must be assessed promptly and treated aggressively.
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 Drug Manual). Work-up may include an assessment of cardiac ejection fraction, and cardiac oncology referral if necessary.
4. **Extravasation**: DOXOrubicin and vinBLAStine cause pain and 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. Refer to BC Cancer Infusion-Related Reactions Guidelines.
6. **Hepatitis B Reactivation**: See SCHBV protocol for more details.

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