

# BC Cancer Protocol Summary for Treatment of Hemophagocytic Lymphohistiocytosis with Etoposide, Dexamethasone and cycloSPORINE

**Protocol Code**

**HLHETCSPA**

**Tumour Group**

**Lymphoma**

**Contact Physician**

**Dr. Luke Chen**

## ELIGIBILITY:

- Clinicopathologic diagnosis of: Hemophagocytic Lymphohistiocytosis (HLH) associated with a malignant lymphoproliferative disorder, according to Histiocyte Society criteria (see Table 1 below)
- Underlying dendritic cell-related disorder or Langerhans cell histiocytosis may or may not be present
- Patients are appropriate candidates for chemotherapy

## TESTS:

- Baseline (required before first treatment): CBC & Diff, INR, aPTT, fibrinogen, bilirubin, ALT, LDH, creatinine
- Baseline (required, but results do not have to be available to proceed with first treatment; results must be checked before proceeding with further treatment): HIV, HBsAg, HBsAb, HBcoreAb, EBV DNA, CMV DNA, ferritin, fasting lipid profile, SPEP and immunoglobulins (IgG, IgA, IgM)  
soluble interleukin-2 receptor (sCD25): order a gold top tube on ice to BC Cancer tumour marker. This test is usually batched and run weekly, but if a STAT result is needed, call 604 707 2836 or 604 707 2828
- Baseline: At the treating physician's discretion, the following tests can be ordered to help the diagnosis and management of HLH. These tests are not available in Vancouver and must be arranged at a specialized center (inpatients require hospital laboratory approval, outpatients require MSP out of province approval):
  - NK function, CD 163, perforin/granzyme b
  - Gene testing for known HLH-associated mutations (generally only done in patients being considered for allogeneic stem cell transplant)
- Weekly: CBC & Diff, bilirubin, creatinine
- Weekly cycloSPORINE trough levels once cycloSPORINE initiated
- If clinically indicated: Weekly, ALT, LDH, ferritin, and CMV and/or EBV DNA levels if positive at baseline.
- If clinically indicated: HBV viral load (see protocol [SCHBV](#))
- Week 3: lumbar puncture with CSF analysis (cell count and differential, protein and glucose)
- Repeat lumbar puncture and CSF analysis at week 4 if initial result is abnormal or at any time if progressive neurological symptoms appear

## PREMEDICATIONS:

None

## SUPPORTIVE MEDICATIONS:

- High risk of hepatitis B reactivation. If HBsAg or HBcoreAb positive, follow hepatitis B prophylaxis as per [SCHBV](#).

## TREATMENT:

### Week 1 and 2:

Drug	Dose	BC Cancer Administration Guideline
etoposide	150 mg/m <sup>2</sup> on day 1, 4, 8, 11	IV in 500 to 1000 mL NS over 45 minutes to 1 hour 30 minutes, using non-DEHP bag and tubing with 0.2 micron in-line filter
dexamethasone	10 mg/m <sup>2</sup> daily	PO or IV push (PO dose round to nearest 2 mg)
cycloSPORINE	3 mg/kg BID, adjusted for target serum trough level 200 mcg/L	PO (round to nearest 25 mg)

### Week 3 to 8:

Drug	Dose	BC Cancer Administration Guideline
etoposide	150 mg/m <sup>2</sup> once weekly	IV in 500 to 1000 mL NS over 45 minutes to 1 hour 30 minutes, using non-DEHP bag and tubing with 0.2 micron in-line filter
dexamethasone	5 mg/m <sup>2</sup> daily week 3 and 4, 2.5 mg/m <sup>2</sup> daily week 5 and 6, 1.25 mg/m <sup>2</sup> daily week 7 and 8	PO or IV push (PO dose round to nearest 0.5 mg)
cycloSPORINE*	3 mg/kg BID, adjusted for target serum trough level 200 mcg/L	PO (round to nearest 25 mg)
methotrexate and hydrocortisone	12 mg methotrexate and 50 mg hydrocortisone	Intrathecal with first lumbar puncture, repeat if CSF abnormal or neurological symptoms due to HLH weekly for four doses total (i.e. week 3, 4, 5, 6) qs to 6 mL with <b>preservative-free</b> NS

**\*Note:** Initiation of cycloSPORINE may need to be delayed until the condition of the patient has stabilized and renal function is improved (CrCl greater than 50 mL/min)

### Procedure for Injecting Chemotherapy into the Intraventricular Space Using an Ommaya Reservoir (By Physician Only)

1. Check that chemotherapy is mixed in **preservative free** normal saline.
2. Use sterile technique, gloves, mask, etc.
3. Have patient in the lying or sitting position.
4. Cleanse skin over the Ommaya reservoir and surrounding scalp with antiseptic after shaving away any recent hair growth.
5. Attach a 25 gauge butterfly needle to a 12 mL syringe.
6. Insert the 25 gauge needle perpendicular to the scalp until the back wall of the reservoir is contacted.
7. Slowly aspirate 6 mL of CSF. Send for cytology and/or culture if appropriate.
8. Attach chemotherapy syringe and inject slowly over about 5 minutes. A more rapid injection frequently causes acute or delayed headaches.
9. To facilitate the flow of the chemotherapy you may gently depress the Ommaya reservoir a few times. Another alternative to flush the system with 1-3 mL of preservative free saline after injecting the chemotherapy. This requires the removal of a similar volume of CSF with the initial CSF withdrawal.
10. Have patient remain at bedrest for 30 minutes after procedure in prone (abdomen down) position.

**Continuation therapy after week 8:** Patients who still have active disease after the initial 8 weeks of therapy should be considered for continuation therapy every 2 weeks. Continuation therapy is typically given as a bridge to allogeneic stem cell therapy.

**Continuation Therapy:**

Drug	Dose	BC Cancer Administration Guideline
etoposide	150 mg/m <sup>2</sup> once every 2 weeks	IV in 500 to 1000 mL NS over 45 minutes to 1 hour 30 minutes, using non-DEHP bag and tubing with 0.2 micron in-line filter
dexamethasone	10 mg/m <sup>2</sup> daily x 3 days every 2 weeks	PO or IV push (PO dose round to nearest 2 mg)
cycloSPORINE	3 mg/kg BID daily, adjusted for target serum trough level 200 mcg/L	PO (round to nearest 25 mg)

**DOSE MODIFICATIONS:**

**1. Hematological:**

Most patients with HLH have severe cytopenias at initiation of therapy and this is generally NOT a contra-indication to initiation of treatment. Deciding whether persistent neutropenia or thrombocytopenia is due to disease or etoposide will depend upon clinical judgement.

**2. Renal dysfunction and/or Hepatic dysfunction<sup>1</sup>:** etoposide only

Creatinine clearance	Bilirubin	Dose modification
greater than 50 mL/min	Any	100%
10 to 50 mL/min	Any	75%
less than 10 mL/min	less than 50 micromol/L	50%
less than 10 mL/min	greater than 50 micromol/L	25%

**3. Renal dysfunction:** cycloSPORINE should be held in patients with creatinine clearance less than 50 mL/min until renal recovery has occurred.

**4. Age and performance status:** At physician's discretion, initial doses of etoposide may be reduced 25 to 50% for age greater than 75 years and poor performance status.

**PRECAUTIONS:**

- Neutropenia:** fever or other evidence of infection must be assessed promptly and treated aggressively.
- Hypersensitivity:** If applicable, monitor etoposide infusion for the first 15 minutes for signs of hypotension. Refer to BC Cancer Hypersensitivity Guidelines- Systemic Therapy Policy IV-10.
- Hepatitis B Reactivation:** See [SCHBV protocol](#) for more details.
- Infection Prophylaxis:** Patients should receive the following for prevention of infection beginning with initiation of treatment and continued until completion of therapy: **Cotrimoxazole DS** one tablet BID every Monday and Thursday, **fluconazole** 200 mg po daily, and **Intravenous immunoglobulin** 0.5 grams/kg monthly. Co-infections (e.g. HIV, CMV) should be appropriately treated when applicable.
- Extravasation:** Etoposide causes irritation if extravasated. Refer to BC Cancer Extravasation Guidelines – Systemic Therapy Policy III-20.

6. **Renal Dysfunction:** Methotrexate, given by any route, should be given with special caution if the creatinine clearance is less than 30 mL/minute with all subsequent doses determined based on hematologic and mucosal tolerance for the first dose given.
7. **Precautions for Intrathecal Administration:** refer to BC Cancer Intrathecal Policy

**Call Dr. Luke Chen or tumour group delegate at (604) 875 4863 with any problems or questions regarding this treatment program.**

**Table 1: Diagnostic criteria for HLH used in the HLH-2004 trial<sup>2</sup>**

<b>A. Molecular diagnosis consistent with HLH: pathologic mutations of PRF1, UNC13D, Munc18-2, Rab27a, STX11, SH2D1A, or BIRC4*</b>
<b>OR</b>
<b>B. Five of the eight criteria listed below:</b>
a. Fever
b. Splenomegaly
c. Cytopenias affecting more than 1 line (Hemoglobin less than 90 g/L, platelet less than 100 x 10 <sup>9</sup> /L, PMNs less than 1.0 x 10 <sup>9</sup> /L)
d. Fasting triglycerides greater than 2.65 g/L or fibrinogen less than 1.5 g/L
e. Hemophagocytosis in bone marrow, spleen, lymph nodes, or liver**
f. Low or absent NK-cell activity
g. Ferritin greater than 500 mcg/L ***
h. Elevated soluble interleukin-2 receptor (sCD25) greater than 2400 U/mL ***

\* Molecular genetic testing is generally done only adult patients being considered for allogeneic stem cell transplant, as non specific mono-allelic variants are common, and true familial disease (known digenic mutations) are very high penetrance and usually present in infancy.

\*\* Hemophagocytosis is often a late feature, and is not necessary for diagnosis of HLH.

\*\*\* Most adults with HLH have a ferritin greater than 3000 mcg/L and a sIL-2r 2400 U/mL (sensitivity 100% for each)<sup>3</sup>

## REFERENCES:

1. Jordan MB, Allen CE, Weitzman S, Filipovich AH, McClain KL. How I treat hemophagocytic lymphohistiocytosis. Blood. 2011;118:4041-4052.
2. Henter JL, Horne A, Arico M, et al. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer. 2007;48:124-131.
3. Hayden A, Lin M, Park S, et al. Soluble interleukin-2 receptor is a sensitive diagnostic test in adult HLH. Blood Adv. 2017;1:2529-2534.