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, platelets, 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, HBcoreAb, EBV DNA, CMV DNA, ferritin, fasting lipid profile, SPEP and immunoglobulins (IgG, IgA, IgM)
- 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, platelets, 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.
- 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:
If HBsAg or HBcoreAb positive, start lamiVUDine 100 mg/day PO for the duration of chemotherapy and for six months afterwards.
**TREATMENT:**

**Week 1 and 2:**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>BC Cancer Administration Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>etoposide</td>
<td>150 mg/m^2 on day 1, 4, 8, 11</td>
<td>IV in 500 to 1000 mL NS over 45 to 90 minutes, using non-DEHP bag and tubing with 0.22 micron or smaller in-line filter</td>
</tr>
<tr>
<td>dexamethasone</td>
<td>10 mg/m^2 daily</td>
<td>PO or IV push (PO dose round to nearest 2 mg)</td>
</tr>
<tr>
<td>cycloSPORINE</td>
<td>3 mg/kg BID, adjusted for target serum trough level 200 mcg/L</td>
<td>PO (round to nearest 25 mg)</td>
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**Week 3 to 8:**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>BC Cancer Administration Guideline</th>
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</thead>
<tbody>
<tr>
<td>etoposide</td>
<td>150 mg/m^2 once weekly</td>
<td>IV in 500 to 1000 mL NS over 45 to 90 minutes, using non-DEHP bag and tubing with 0.22 micron or smaller in-line filter</td>
</tr>
<tr>
<td>dexamethasone</td>
<td>5 mg/m^2 daily week 3 and 4, 2.5 mg/m^2 daily week 5 and 6, 1.25 mg/m^2 daily week 7 and 8</td>
<td>PO or IV push (PO dose round to nearest 0.5 mg)</td>
</tr>
<tr>
<td>cycloSPORINE*</td>
<td>3 mg/kg BID, adjusted for target serum trough level 200 mcg/L</td>
<td>PO (round to nearest 25 mg)</td>
</tr>
<tr>
<td>methotrexate and hydrocortisone</td>
<td>12 mg methotrexate and 50 mg hydrocortisone</td>
<td>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 preservative-free NS</td>
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*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:

<table>
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<tr>
<th>Drug</th>
<th>Dose</th>
<th>BC Cancer Administration Guideline</th>
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<tbody>
<tr>
<td>etoposide</td>
<td>150 mg/m² once every 2 weeks</td>
<td>IV in 500 mL NS over 45 minutes, using non-DEHP bag and tubing with 0.22 micron or smaller in-line filter</td>
</tr>
<tr>
<td>dexamethasone</td>
<td>10 mg/m² daily x 3 days every 2 weeks</td>
<td>PO or IV push (PO dose round to nearest 2 mg)</td>
</tr>
<tr>
<td>cycloSPORINE</td>
<td>3 mg/kg BID daily, adjusted for target serum trough level 200 mcg/L</td>
<td>PO (round to nearest 25 mg)</td>
</tr>
</tbody>
</table>

DOSE MODIFICATIONS:
1. Hematological:

Most patients with HLH have severe cytopenias at initiation of therapy and this is generally NOT a contraindication 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:

   - etoposide only

<table>
<thead>
<tr>
<th>Creatinine clearance</th>
<th>Bilirubin</th>
<th>Dose modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>greater than 50 mL/min</td>
<td>Any</td>
<td>100%</td>
</tr>
<tr>
<td>10 to 50 mL/min</td>
<td>Any</td>
<td>75%</td>
</tr>
<tr>
<td>less than 10 mL/min</td>
<td>less than 50 micromol/L</td>
<td>50%</td>
</tr>
<tr>
<td>less than 10 mL/min</td>
<td>greater than 50 micromol/L</td>
<td>25%</td>
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</table>

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:
1. Neutropenia: fever or other evidence of infection must be assessed promptly and treated aggressively.
2. 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.
3. 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 for six months afterwards. 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.
4. 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.


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

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

* 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)³

**REFERENCES:**

