IWK guidance document for physicians for the management of blinatumomab for children with cancer in Advanced Centers in the Maritimes.

Fever management for a child receiving a blinatumomab cycle:

Patient must be within one hour of the advanced center during blinatumomab cycles.

a) **If the child is not neutropenic and well:** Obtain a blood culture from all lumens of the CVAD and draw a CBCD and labs then give a dose of ceftriaxone within one hour of arrival at the hospital. The patient will need to be admitted for at least 24 hours. Call the pediatric hematologist/oncologist within an hour of the patient arriving at the hospital.

b) **If the child is not neutropenic but is unwell:** Obtain a blood culture from all lumens of the CVAD and draw a CBCD and labs and start anti-pseudomonal beta lactam either piperacillin/tazobactam or cefepime within one hour of arrival at the hospital as per the patient's treat promptly card. The patient will need to be admitted for at least 24 hours. Call the pediatric hematologist/oncologist within an hour of the patient arriving at the hospital.

c) **If the child is neutropenic:** Follow the APPHON febrile neutropenia guideline and call the pediatric hematologist/oncologist within an hour of the patient arriving at the hospital.

d) **If the CBCD is not reported within an hour of arrival** of the patient at the hospital administer a dose of piperacillin/tazobactam.

Note: It is known that children receiving blinatumomab have a 10% higher incidence of catheter related infections likely thought to be due to the continuous administration of the drug over 28 days. If you see pus at the catheter site, swab.

If the child has a blood culture that results positive, draw a repeat blood culture and call the pediatric hematologist/oncologist; the patient will need to be transferred to the IWK.

It is not necessary to insert a peripheral intravenous line for administration over the short term. It is permitted to interrupt the infusion to administer the antibiotic.

Blinatumomab Blocks Hospitalization:

- For interruptions in the blinatumomab infusion for greater than 4 hours, hospitalization for 24 hours for observation is required. Premedication with reinitiation of blinatumomab is not required.
- For any child with a fever regardless of neutrophil count, hospitalization for at least 24 hours for antibiotics and observation is required.

When to stop blinatumomab infusion:

- Cytokine release syndrome is grade 2 or greater.
- For any seizure event.
- Other neurological toxicities such as encephalopathy, confusion or significant somnolence or agitation.
- Grade 3 or greater: any other AEs occur (except cytopenias and metabolic

derangements that respond to treatment).
- It is permitted to stop blinatumomab in the event of breakage of the blinatumomab line and/or the blinatumomab bag. It is permitted to wait until the next morning to hang a new bag of blinatumomab.

Blinatumomab troubleshooting:

1. Air in the line: APHON or adult chemotherapy nurse.
2. Line/bag leakage: 2 APHON trained nurses to hang a new bag.
3. Antibiotics: APHON or adult chemotherapy nurse.

If number 2 is not an option, transfer the patient to the IWK with the backup blinatumomab bag.

If number 3 is not an option for every 6-hour antibiotics it is permitted to switch the blinatumomab to a peripheral intravenous line. If this is done when you switch the blinatumomab back to the central line it has to be with a new bag.

If the patient arrives overnight, it is permitted to restart the blinatumomab in the morning when more staff are available.

Blinatumomab adverse reactions and management:

1) **Cytokine release syndrome:**

The most frequent serious adverse events found in patients treated with blinatumomab are systemic cytokine release syndrome (CRS) and disorders of the nervous system. Both categories of events are more likely to occur within the first week of treatment with blinatumomab, and both categories of events are usually reversible and able to be managed with attentive supportive care.

Clinical signs and symptoms of CRS include fever, hypoxia and hypotension; see table below for grading of severity. Clinical signs and symptoms of neurotoxicity include the following: headache, tremor; apraxia, aphasia, ataxia; dizziness, confusion, disorientation; reversible seizures; encephalopathy; somnolence/agitation.

Patients who have an interruption in blinatumomab and are admitted to restart blinatumomab cycles should as a minimum have vital signs every 4 hours, including pulse oximeter and a daily age-appropriate focused neurological assessment with finger-nose-finger, a writing sample, or pointing to named stickers (as age-appropriate) is required.

For that majority of patients, CRS can be managed by discontinuing the infusion and with supportive care. For the rare patients with grade 3 or higher CRS consider dexamethasone or tocilizumab. For grade 3 or higher neurotoxicity consider dexamethasone.

Dexamethasone: IV preferred

- Total daily dose: 0.02 – 0.04 mg/kg/day (maximum 24 mg per day) divided into 3-4 doses daily for at least one day, but no more than 4 days. Dose should then be stopped or tapered as clinically indicated.

Tocilizumab: IV infusion

- Patient weight < 30 kg: 12 mg/kg IV over 1 hour
- Patient weight > 30 kg: 8 mg/kg IV over 1 hour (max dose 800 mg)

Cytokine Release Syndrome Grading System*

Grade*	Symptoms
Grade 1	Fever with or without constitutional symptoms (e.g. rigors, headache, fatigue, malaise, nausea, vomiting, myalgia, arthralgia) – Responds to Symptomatic Treatment
Grade 2	Fever with or without constitutional symptoms AND: Hypoxia responding to supplemental O2 of less than 40%, OR Hypotension responsive to fluid management
Grade 3	Fever with or without constitutional symptoms AND: Hypoxia requiring supplemental O2 of greater than 40%, OR Hypotension requiring one vasopressor
Grade 4	Life-threatening symptoms Ventilator or multiple pressor supports required
Grade 5	Death

* This table is based on CTCAEv5

2) **Neurotoxicity:**

Neurotoxicity is rare but if it occurs it is usually within the first 2 weeks. Symptoms can include disturbance or loss of movement of parts of the body, speech/coordination disorders, confusion, disorientation, dizziness, trembling, apraxia, seizures, encephalopathy, somnolence and agitation.

In the event of a seizure, stop the blinatumomab and manage the patient.

3) **Infusion related reaction/hypersensitivity:**

Symptoms present very similar to CRS so most of the time the management is as per the CRS management in the first bullet. If determine the reaction is not CRS manage the IRR/hypersensitivity reaction as you would any other drug reaction.

4) **Transaminitis:**

Elevations in liver enzymes can occur usually in first few days of starting a cycle of blinatumomab but can last a few weeks. Infrequently adjustments in treatment may be required.

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