BC Cancer Protocol Summary for Treatment of Pre-B-Cell Acute Lymphoblastic Leukemia with Minimal Residual Disease using Blinatumomab

Protocol Code	*ULKMRDBLIN*
Tumour Group	*Leukemia/BMT*
Contact Physician	*Dr. Yasser Abou Mourad*

ELIGIBILITY:

Patients must have:
- B-cell precursor acute lymphoblastic leukemia (ALL),
- Philadelphia chromosome (Ph)-negative and CD19 positive disease,
- Achieved and be in first or second complete hematologic remission (CR),
- Minimal (measurable) residual disease (MRD) detected at a level greater than or equal to 10^{-3} (0.1%),
- Completed minimum of 3 cycles of curative intent chemotherapy,
- Treatment prescribed by Leukemia/BMT Program physicians and delivered at Vancouver General Hospital, and
- BC Cancer "Compassionate Access Program" approval prior to treatment (please refer to https://cap.phsa.ca/).

Patients should have:
- ECOG 0 to 2
- Adequate hematologic, renal and hepatic function
- Available social support and ability to safely receive blinatumomab via an out-patient pump

Note:
- Patients can proceed to allogeneic hematopoietic stem cell transplantation any time after cycle 1.

EXCLUSIONS:

Patients must not have:
- MRD negative or MRD unknown disease,
- Ph+ ALL,
- Prior treatment with blinatumomab, or
- Prior allogeneic hematopoietic stem cell transplantation (HSCT)

TESTS:

- Baseline: CBC with diff, electrolytes, uric acid, phosphate, calcium, urea, creatinine, ALT, ALP, GGT, bilirubin, albumin, LDH

Cycle 1:

- Daily while an inpatient then at each outpatient visit: CBC with diff, sodium, potassium, uric acid, phosphate, calcium, urea, creatinine, ALT, ALP, GGT, bilirubin, albumin, LDH.
- Twice weekly while an inpatient, then at each outpatient visit: Amylase, lipase
- Daily while an inpatient: INR, fibrinogen, serum CRP daily

Cycles 2 to 4:

- Before cycle 2: INR, fibrinogen, serum CRP
- Daily while an inpatient then at each outpatient visit: CBC with diff, electrolytes, uric acid, phosphate, calcium, urea, creatinine, ALT, ALP, GGT, bilirubin, albumin, LDH.
- Twice weekly while an inpatient, then at each outpatient visit: amylase, lipase

SUPPORTIVE MEDICATIONS

- cotrimoxazole DS 1 tablet PO BID every Monday and Thursday
- If HSV seropositive, valACYclovir 500 mg PO BID
- If HBsAg or HBcoreAb positive, start lamiVUDine 100 mg PO daily for the duration of chemotherapy and continue for one year from treatment completion for patients who are HBsAg positive and for six months for patients who are HBcoreAb positive.

PREMEDICATIONS:

- dexamethasone 20 mg IV one hour before blinatumomab infusion on Day 1
- acetaminophen 650 mg PO 30 minutes before blinatumomab infusion on Day 1
- diphenhydrAMINE 25 mg or 50 mg IV 30 minutes before blinatumomab infusion on Day 1

PREHYDRATION

Cycles 1 and 2: NS IV at 100 mL/h starting on Day 1 and reassess after Day 3

TREATMENT

Each treatment cycle is 6 weeks. Hospitalization is recommended at a minimum for the first 3 days of cycle 1 and the first 2 days of cycle 2. Subsequent cycles may be started as an outpatient.

Schema

Cycles 1 to 4:

Drug	Weeks 1 to 4	Week 5	Week 6
blinatumomab*	28 mcg/day for 28 days	rest	rest

*blinatumomab (fixed dose) is for patients greater than or equal to 45 kg

- Blinatumomab is administered as a continuous infusion on days 1 to 28, followed by a 2-week rest period. Each cycle is 6 weeks.
- Treatment consists of one induction cycle followed by up to 3 consolidation cycles (maximum 4 cycles)
- Treatment should be continued until unacceptable toxicity, hematologic relapse, MRD relapse, treatment with hematopoietic stem cell transplant (HSCT), or up to the completion of four cycles, whichever comes first.

Cycle 1

Vital signs before blinatumomab infusion on Day 1, every hour for first 4 hours of infusion and every 2 hours for next 4 hours. If stable, then routine vital signs.

Drug	Dose	BC Cancer Administration Guideline
blinatumomab	28 mcg on days 1 to 4	IV in NS 250 mL over 24 hours at 10 mL/h
	112 mcg on days 5, 9, 13, 17, 21, 25*	IV in NS 250 mL over 96 hours at 2.5 mL/h

*Patients need to return to clinic on day 29 for bag removal

Cycles 2 to 4

- Cycle 2: Vital signs before infusion starts on Day 1, every hour for first 4 hours of infusion and every 2 hours for next 4 hours. It stable, then routine vital signs.
- Cycles 3 and 4: Vital signs routine.

Drug	Dose	BC Cancer Administration Guideline
blinatumomab	112 mcg on days 1, 5, 9, 13, 17, 21, 25*	IV in NS 250 mL over 96 hours at 2.5 mL/h

* Patients need to return to clinic on day 29 for bag removal

Special notes on preparation and administration

1. Prepare with non-DEHP bag and administer via CADD pump with non-DEHP tubing and 0.2 micron in-line filter.
2. Infuse ONLY 240 mL because each bag is prepared with excess drug.
3. Prime IV line with blinatumomab only via CADD pump. Do not prime with NS. Do not prime using gravity.
4. Change bag at the same time each day. Discard any remaining IV solution.
5. Use a dedicated IV line. Do not flush the infusion line for any reason.

DOSE MODIFICATIONS

If the interruption after an adverse event is 7 days or less, continue the same cycle to a total of 28 days of infusion inclusive of days before and after the interruption in that cycle. If an interruption due to an adverse event is longer than 7 days, start a new cycle.

1. Infusion interruption

Interruption	Management
1 to 4 hours	May resume at physician's discretion
More than 4 hours	Repeat dexamethasone 16 mg IV 60 minutes prior to restarting the infusion. Lower dose may be considered but not required.

2. Cytokine release syndrome

	Management
Grade 3	Hold until Grade 1. Resume at 9 mcg/day and increase to 28 mcg/day after 7 days if toxicity does not recur
Grade 4	Discontinue blinatumomab

3. Neurologic events

	Management
Grade 3	Hold until Grade 1 and for at least 3 days. Resume at 9 mcg/day and increase to 28 mcg/day after 7 days if the toxicity does not recur. For reinitiation, premedicate with up to 24 mg of dexamethasone with a 4-day taper. As secondary prophylaxis, consider appropriate anticonvulsant medication. If the toxicity occurred at 9 mcg/day, or if the toxicity takes more than 7 days to resolve, discontinue blinatumomab.
Grade 4 or more than one seizure	Discontinue blinatumomab

4. Other adverse reactions

	Management
Grade 3	Hold until Grade 1 or baseline. Resume at 9 mcg/day and increase to 28 mcg/day after 7 days if the toxicity does not recur. Discontinue if toxicity takes more than 14 days to resolve.
Grade 4	Consider discontinuing blinatumomab permanently.

PRECAUTIONS:

1. **Cytokine release syndrome:** For treatment, consider dexamethasone IV 8 mg q8h for 3 days, then 8 mg q12h for 2 days, then 8 mg once daily for 1 day, then 4 mg once daily for 1 day.
2. **Infusion Reactions,** including anaphylaxis, may occur within 24 hours of infusion, usually with the first infusion and decreasing with subsequent infusions. Risk factors include a high tumour burden. Infusion reactions may require rate reduction, interruption of therapy, or treatment discontinuation. Hospitalization is recommended at a minimum for the first 3 days of cycle 1 and for the first 2 days of cycle 2.
3. **Neurologic events:** Elderly patients (65 years and older) are at higher risk of developing neurological events, including cognitive impairment, encephalopathy, seizures, speech disorders, coordination and balance disorders, and confusion.
4. **Infections:** Consider anti-fungal prophylaxis with fluconazole or other antifungal for patients with neutropenia, or prior invasive fungal infection. For patients who are HSV seronegative, but have an indication for shingles prophylaxis (e.g. history of shingles, etc), give prophylaxis with valACYclovir.
5. **CNS prophylaxis:** Intrathecal chemoprophylaxis is recommended prior to starting blinatumomab and following each cycle of blinatumomab.
6. **Current relevant CNS pathology**: may increase risk of neurotoxicity. Additional monitoring recommended.

Call Dr. Yasser Abou Mourad (Leukemia/BMT) or tumour group delegate at (604) 875-4337 with any problems or questions regarding this treatment program.

References:

1. Gökbuget N, Dombret H, Bonifacio M et al. Blinatumomab for minimal residual disease in adults with B-cell precursor acute lymphoblastic leukemia. Blood 2018;5;131:1522–1531.
2. Amgen Canada Inc. Blinatumomab Product Monograph. Mississauga, Ontario; 6 May 2021.