BC Cancer Protocol Summary for Treatment of Acute Myeloid Leukemia using Gemtuzumab Ozogamicin with Induction and Consolidation Chemotherapy

Protocol Code	*LKGEMOZ*
Tumour Group	*Leukemia/BMT*
Contact Physician	*Dr. David Sanford*

ELIGIBILITY:

- Adult patients with previously untreated, de novo CD 33-positive acute myeloid leukemia (AML), except acute promyelocytic leukemia (APL)
- Have favourable, intermediate, or unknown cytogenetics (using European LeukemiaNet (ELN) 2017 risk classification)
  - In the event where the patient's cytogenetic status is unknown (that is, because the test was unsuccessful) or when their cytogenetic test results are not yet available, gemtuzumab ozogamicin could be initiated at induction therapy
  - should a patient's unknown cytogenetics become known as adverse, gemtuzumab ozogamicin should be discontinued
- ECOG performance status 0-2
- Use of gemtuzumab ozogamicin in combination with
  - cytarabine and DAUNOrubicin (7 plus 3) induction chemotherapy: only **one** cycle is eligible
  - high dose cytarabine (HIDAC) or intermediate dose cytarabine (INDAC) consolidation chemotherapy: up to two cycles are eligible
- Prescribed by Leukemia/BMT Program physicians

EXCLUSIONS:

- Therapy-related AML
- Adverse cytogenetics (using European LeukemiaNet (ELN) 2017 risk classification)
- FLT3-ITD or TKD positive AML planned for treatment with midostaurin
  - In the event where the patient's FLT3 status is unknown (that is, because the test was unsuccessful) or when their FLT3 test results are not yet available, gemtuzumab ozogamicin could be initiated at induction therapy
- Cirrhosis, chronic hepatitis, or clinically significant liver disease
- Pregnancy

TESTS:

- Baseline, before each gemtuzumab ozogamicin treatment, and as clinically indicated: CBC & differential, platelets, bilirubin (total and direct), ALT, alkaline phosphatase, LDH, GGT, albumin, sodium, potassium, magnesium, calcium, phosphate, urea, creatinine
- Before Day 1: INR, PTT, fibrinogen
- Baseline and if clinically indicated: ECG, bone marrow biopsy, lumbar puncture
- Required, but results do not have to be available to proceed with first treatment; results must be checked before proceeding with next treatment: HBsAg, HBcoreAb

SUPPORTIVE MEDICATIONS:

- If HBsAg or HBcoreAb positive, start lamiVUDine 100 mg PO daily for the duration of chemotherapy treatment and for six months afterwards
- If HSV seropositive, start valACYclovir 500 mg PO BID
- Refer to current Leukemia/BMT program recommendations for antifungal and antibiotic prophylaxis during neutropenic period (ANC less than 0.5 x 10^9/L) following chemotherapy
- Consider ursodiol for venoocclusive disease (VOD)/sinusoidal obstruction syndrome (SOS) prophylaxis
- dexamethasone 0.1% ophthalmic drops: 2 drops in each eye q6h starting immediately before the first dose of cytarabine and continue until 48 hours after the last dose of cytarabine in consolidation cycles with HIDAC/INDAC

PREMEDICATIONS:

- Consider antiemetic protocol for moderately emetogenic chemotherapy (see SCNAUSEA).
- To prevent infusion-related reactions:
  - dexamethasone 12 mg IV 1 hour prior to gemtuzumab ozogamicin
  - diphenhydrAMINE 50 mg PO 1 hour prior to gemtuzumab ozogamicin
  - acetaminophen 650 mg PO 1 hour prior to gemtuzumab ozogamicin

TREATMENT:

- **Induction:**

Drug	Dose	BC Cancer Administration Guideline
cytarabine	100 mg/m^2 on Days 1 to 7	IV in 500 mL D5W over 24 hours
DAUNOrubicin*†	60 mg/m^2 on Days 1 to 3	IV in 100 mL D5W over 30 minutes
gemtuzumab ozogamicin**†	3 mg/m^2 (max 4.5 mg) on Days 1, 4 and 7	IV in 25 to 50 mL NS over 2 hours Using a 0.2 micron in-line filter Observe for 60 minutes post-infusion

** dose may be decreased to 45 mg/m^2 or administered for 2 days for second induction*
***do NOT give gemtuzumab ozogamicin if a second induction is needed*
† see Dose Modifications for alternative schedule utilized in leukoreduction

When used in combination with cytarabine and DAUNOrubicin (7 plus 3) induction chemotherapy, only **one** cycle of gemtuzumab ozogamicin is eligible.

- **Consolidation:**

Drug	Dose	BC Cancer Administration Guideline
cytarabine	Up to 60 years of age (HIDAC): 3000 mg/m^2 on Days 1 to 6 Over 60 years of age (INDAC): 1000 mg/m^2 on Days 1 to 5	IV in 250 mL D5W over 3 hours IV in 100 mL D5W over 2 hours
gemtuzumab ozogamicin	3 mg/m^2 (max 4.5 mg) on Day 1	IV in 25 to 50 mL NS over 2 hours Using a 0.2 micron in-line filter Observe for 60 minutes post-infusion

When used in combination with high dose cytarabine (HIDAC) or intermediate dose cytarabine (INDAC) consolidation chemotherapy, up to two cycles of gemtuzumab ozogamicin are eligible.

DOSE MODIFICATIONS:

1. **Hematology:**
   If neutrophil and platelet counts do not recover within 14 days following the planned start date of the consolidation cycle, discontinue gemtuzumab ozogamicin in consolidation cycles.

   For gemtuzumab ozogamicin in consolidation:

ANC (x 10^9/L)		Platelets (x 10^9/L)	Dose
greater than or equal to 0.5	and	greater than or equal to 100	100%
less than 0.5	or	less than 100	Discontinue

2. **Hepatic Toxicity:** Delay treatment with gemtuzumab ozogamicin until total bilirubin less than or equal to 2 x ULN and ALT less than or equal to 2.5 x ULN. If VOD/SOS develops, permanently discontinue gemtuzumab ozogamicin.

3. **Infusion-Related Reactions:** Follow SCDRUGRX for immediate clinical management. For severe or life-threatening reactions, permanently discontinue gemtuzumab ozogamicin.

4. **Renal Impairment:** No dose adjustment required in patients with mild to moderate renal impairment (CrCl 30 mL/min or greater). Has not been studied in patients with severe renal impairment (CrCl below 30 mL/min) or end stage renal disease.

5. **Leukoreduction**: For patients with hyperleukocytosis (WBC greater than 30,000 mm^3), leukoreduction with cytarabine with or without hydroxyUREA may be utilized in induction.

   Alternative schedule for leukoreduction in induction:

Drug	hydroxyUREA	cytarabine	DAUNOrubicin	gemtuzumab ozogamicin
Administration Days	Day 1	Days 1 to 7	Days 3 to 5	Days 3, 6, and 9

PRECAUTIONS:

1. **Infusion-related reactions**: Life-threatening reactions, including anaphylaxis, have been reported. Fever, chills, hypotension, tachycardia, and respiratory symptoms may occur during the infusion or within 24 hours following the infusion. Premedication with a corticosteroid, antihistamine, and acetaminophen is recommended prior to each dose of gemtuzumab ozogamicin. Patients should be monitored during infusion and for at least 1 hour following infusion. For management of infusion-related reactions, see BC Cancer Protocol SCDRUGRX Management of Infusion-Related Reactions to Systemic Therapy Agents.
2. **Tumour Lysis Syndrome (TLS):** Fatal events complicated by acute renal failure have been reported. For patients with hyperleukocytosis, consider leukoreduction with leukapheresis, hydroxyUREA, or cytarabine with or without hydroxyUREA to reduce peripheral WBC below 30,000/mm^3, starting 48 hours prior to initiating gemtuzumab ozogamicin. Patients at risk of TLS should receive adequate hydration, antihyperuricemic prophylaxis and close monitoring.
3. **Venoocclusive Disease (VOD)/Sinusoidal Obstruction Syndrome (SOS):** Fatal hepatotoxicity events including VOD/SOS have been reported. Patients with moderate or severe hepatic impairment are at increased risk. Monitor all patients closely for elevations in liver tests, hepatomegaly, rapid weight gain, and ascites. Patients proceeding to hematopoietic stem cell transplant (HSCT) are recommended to have at least a 2 month interval between the last dose of gemtuzumab ozogamicin and HSCT, should receive VOD/SOS prophylaxis with ursodiol and be closely monitored post-HSCT for development of VOD/SOS.
4. **Myelosuppression:** Life-threatening or fatal infections and hemorrhagic events associated with myelosuppression have been reported. Prolonged thrombocytopenia requiring platelet transfusions has been reported. Monitor complete blood counts prior to and following each gemtuzumab ozogamicin dose until resolution of cytopenias. Treatment interruption or permanent discontinuation of gemtuzumab ozogamicin may be required for severe or persistent myelosuppression.
5. **QTc prolongation**: has been reported; monitor ECG and electrolytes in patients with known risk factors.

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

References:

1. Castaigne S, Pautas C, Terre C et al. Effects of gemtuzumab ozogamicin on survival of adult patients with de-novo acute myeloid leukaemia (ALFA-0701): a randomised, open-label, phase 3 study. Lancet 2012;379(9825):1508-16.
2. Pfizer Canada: MYLOTARG gemtuzumab ozogamicin product monograph. Kirkland, Quebec: 28 November, 2019.
3. The Leukemia/Bone Marrow Transplant Program of BC. Healthcare Professionals Cancer Management Guidelines Acute Myeloid Leukemia (AML). Vancouver, BC: February, 2020.