Blina

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Disclosures

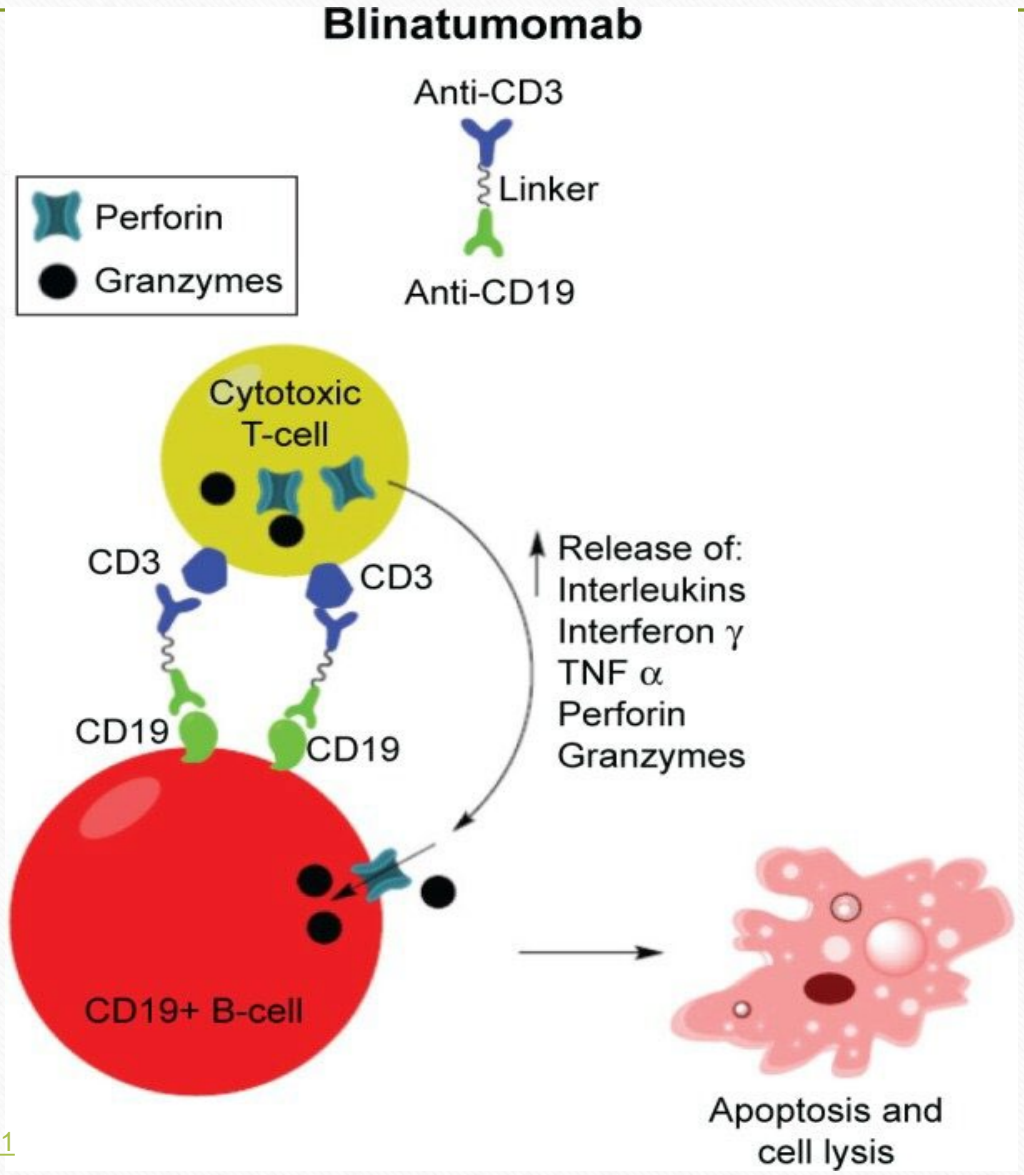
- None

Objectives

- Discuss Blinatumomab
  - Briefly review mechanism of action
- Most common adverse events
  - Cytokine Release Syndrome
  - Neurotoxicity
  - Hypogammaglobulinemia
- Indications, proven – now standard of care in pediatric oncology

B-lin-atu-mo-mab
'B-lineage-specific antitumor mouse monoclonal antibody'.

What is a bispecific T-cell engager (BiTE)-blinatumomab:
Blinatumomab consists of two single chain variable fragments (parts of immunoglobulins) where one binds to CD3 and the other to CD19 with a flexible linker made of short chain of amino acids.



Lee KJ et al. Therapeutics and Clinical Risk Management. 2016. DOI:10.2147/TCRM.S84261

How does blinatumomab work:

- CD19 is a protein found on the surface of most B cells.
- The CD19 fragment of blinatumomab finds the CD19 antigen on the surface of the B cell and activates the killer T cell by attaching to the CD3 protein on its surface.
- The cytotoxic T cell uses perforin to enter the B cell and then release cytotoxic granules (granzymes), and cytokines that lyse the cell and stimulates T-cell proliferation which results in serial killing.
- The therapeutic effect depends on 3 key points: T-cell activity, T-cell to target B-cell ratio and time to form a cytolytic synapse.

Pharmacokinetics of blinatumomab: Absorption, distribution and metabolism.

Absorption:

- Size 504 amino acids about 1/3 smaller than most antibodies this allows better intra-tumor penetration.
- 55 kDa – high molecular weight reduces its penetration across BBB.

Distribution:

- Limited volume of distribution similar to plasma volume.

Metabolism:

- Poorly understood – degraded to small peptides and amino acids by cellular catabolic pathways like other monoclonal abs.

Pharmacokinetics of blinatumomab: Elimination/Clearance

- Linear pharmacokinetics – means clearance does not change with dose.
- Systemic clearance is not affected by creatinine clearance, age or gender, weight.
- < 45 kg dose based on BSA and > 45 kg fixed dosing as BSA dosing above 45 kg showed higher toxicity.
- Blinatumomab activates more than one T cell at a time so B cells are depleted quickly.
- 50% of B cell reduction first hour after infusion initiated and 90% 4 hours into infusion.
- Broken down into simple amino acids quickly due to the smaller size of the molecule results in short half life approximately 2 hours which means it has to be administered by continuous infusion.
- It is given for 4 weeks for maximum antitumor effect with 2 weeks rest to prevent T-cell exhaustion.
- ***Good news: Amgen has produced a subcutaneous product which will be given 3 times per week!***

Drug interactions

- Occurs within the first couple of weeks as higher levels of IL-6 induces inhibition of CYP activity.
- Drugs with narrow therapeutic index are of concern that require CYP for metabolism.

Most common adverse effects of blinatumomab

- Cytokine release syndrome CRS – 11-12% with < 1% (Grade 3 or higher) can be indistinguishable with infusion related reactions ~30% and hypersensitivity reaction with neutralizing antibodies 1-2%.
- Neurotoxicity – ~25%
- Hypogammaglobinemia – ~15%

Cytokine release syndrome

- Blinatumomab triggers the activation of cytotoxic T cells and cytokine release (mostly IL-6, IL-10 & IFNy) over first few days until B cells reduce.
- Patients with elevated LDH or a high tumour burden are at a greater risk.
- Symptoms: pyrexia, headache, nausea, asthenia, hypotension, and increased transaminases or total bilirubin.
- CRS has also been associated with DIC, capillary leak syndrome, and HLH/MAC.
- Pretreating with dexamethasone prior to blinatumomab therapy. Management of CRS may require temporary interruption or discontinuation of blinatumomab.

CRS Grading System

Toxicity Grade	Clinical Picture	Management
Grade 1	Mild: flu-like symptoms, fever, myalgia	• **Supportive care** • **Anti-pyretics**
Grade 2	Moderate: some signs or organ dysfunction (e.g. grade 2 creatinine. grade 3 LFTs)	• **Hospitalization** • **IV therapies**
Grade 3	Severe: increasing sign of organ dysfunction (e.g. grade 3 creatinine. grade 4 LFTs, hypotension, coagulopathy, hypoxia	• **IV fluids or low-dose pressors** • **FFP or cryoprecipitate for coagulopathy** • **Supplemental O2** • **Consider anti IL6 - Tocilizumab**
Grade 4	**Life threatening: Significant hypotension, significant hypoxia**	• **Multiple pressors** • **Mechanical ventilation** • **Anti IL6 – Tocilizumab**

Neurotoxicity

- Generally occurs within 9 days of administration and is most often reversible.
- Mechanism not well described possibly due to T cell reorganization from the peripheral blood into the perivascular space.
- **With temporary** disturbances in CNS function you may see:
  - Disturbance or loss of movement of parts of the body, speech/coordination disorders
  - Confusion, disorientation, dizziness, trembling, apraxia
  - **Reversible seizures**
  - Encephalopathy
  - Somnolence, agitation

Management of neurotoxicity

- You can STOP the Blinatumomab
- Seizures – treat with dexamethasone, anticonvulsants
- Investigate other potential causes of symptoms (imaging)
- Possibly resume post seizure
- Some populations might require seizure prophylaxis (COG protocols recommend seizure prophylaxis for patients with Down Syndrome who are greater than 10 years old)

Hypogammaglobulinemia

- Hypogammaglobulinemia is caused be a depletion of B-cell levels.
- Immunoglobulin M, A and G are effected due to the reduction/elimination of CD19 B cells.
- The consequence of this adverse effect is the risk of infection.
- IgG levels should be monitored monthly and replaced if low.
- B cell recovery usually occurs around 6-9 months after completion of blinatumomab but can be longer.

COG Clinical trial results

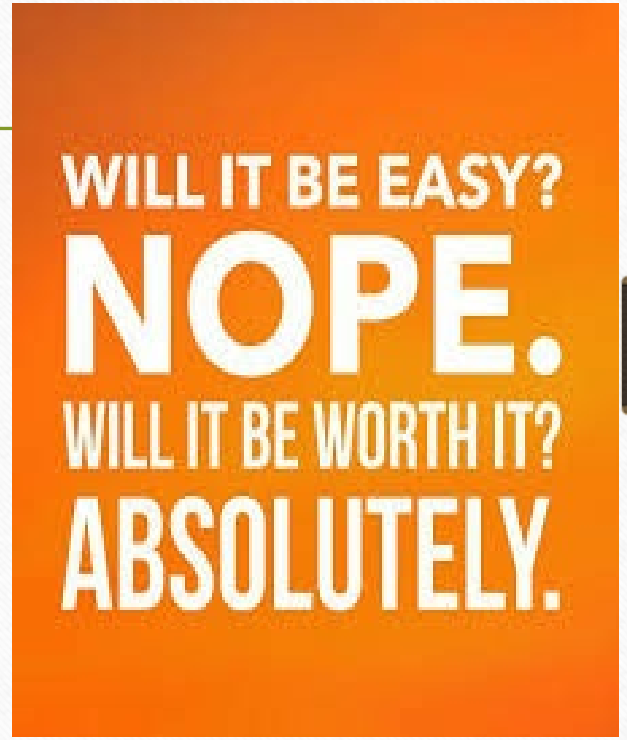
- AALL1331 – relapse ALL trial determined that relapse B cell ALL children benefitted from blinatumomab except for those who had isolated CNS relapses.
- AALL1731 – recent up front ALL trial closed due to superior outcomes in the experimental or blinatumomab arm. This included MRD positive and negative children.
- AALL1731 included all children less than 10 years with ALL and the experimental arm included all children except those that have favorable risk B-ALL and an already established outcome of > 95% - these children will not receive blinatumomab and all others will.
- AALL1731 included HR ALL children and as such blinatumomab will be given to HR B-cell ALL children except those with favorable risk classification.

Recommendations

- All relapse children with B cell ALL, except those with isolated CNS relapse will receive 3 cycles of non-sequential blinatumomab.
- All children over the age of 1 year with B cell ALL (including Philadelphia positive patients) without favorable risk disease will receive 2 non-sequential cycles of blinatumomab except for Down Syndrome who will receive 3 cycles of blinatumomab with reduced systemic therapy.
- Infants with B cell ALL who have unfavorable cytogenetics will receive a cycle of blinatumomab (at the IWK).

Standard of Care

- Approximately 20-25 children are diagnosed in the Maritimes with B-cell ALL per year with ~1 relapse per year.
- About 2/3 of these will receive blinatumomab = ~15 children.
- Blinatumomab is now standard of care in the treatment of most children with B cell ALL.



Note: Provincial coverage is approved case by case at 50% and Amgen 50%.