Blinatumomab Prior to CAR T-Cell Therapy: Literature Review

Background

While chimeric antigen receptor (CAR) T-cell therapy has already been a breakthrough for certain blood cancers, and has been available in Canada since 2019, it is still in early phases of adoption with continued research to improve effectiveness, manage side effects, and expand use. In 2024, questions emerged in Ontario regarding the use of blinatumomab prior to CAR T-cell therapy in patients with acute lymphoblastic leukemia (ALL), with the concern that blinatumomab may limit CAR T-cell expansion and long-term outcomes. Ontario's Transplantation and Cellular Therapy Advisory Committee recommended establishing a working group to review the evidence and provide further guidance.

The working group aimed to describe the evidence about the role and effect of blinatumomab on patients with ALL prior to an anti-CD19 CAR T-cell therapy.

Methodology

A literature review was conducted using MEDLINE and Embase databases from 2018 to the date of search (September 10, 2024). Grey literature was also searched which included an open Google search, advanced Google search, Google Scholar, and DuckDuckGo.com, as well as site-specific hand searches.

A two-phase screening process was used to determine eligibility. In phase I, two independent reviewers screened citation titles and abstracts to determine potential eligibility. Screening was conducted using the eligibility criteria as outlined in **Table 1**. Those deemed potentially eligible in phase I moved to phase II for a full-text review. Phase II was completed by one reviewer.

Data from relevant articles were extracted into an evidence table and stratified according to study design (**Table 2**). The accuracy of the evidence table was verified by a second reviewer.

Table 1: Screening Eligibility Criteria

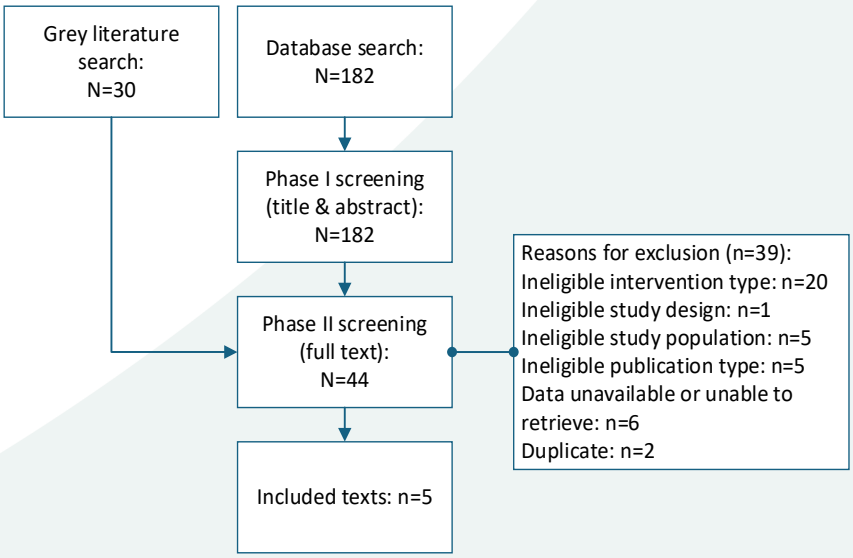
Inclusion Criteria	Exclusion Criteria
Population: adult patients (18 years and older) receiving blinatumomab prior to an anti-CD19 CAR T-cell therapy for ALL **Study designs:** case series, case study, randomized controlled trial (RCT), cohort, case-control **Intervention:** blinatumomab prior to anti-CD19 CAR T-cell therapy **Outcome measures:** treatment response rate, complete remission, MRD conversion rate, proportion of patients who received blinatumomab and made it to CAR T, CAR T response rate (overall survival, progression-free survival) **Publication types:** peer-reviewed literature, abstracts **Language:** English	**Population:** Animal or cadaveric studies **Publication types:** theses, conference proceedings, news

A working group of clinical experts in the field of acute leukemia and CAR T-cell therapy was convened. Working group member names and affiliations are listed in **Appendix A**. The purpose of the working group was to review the evidence and, together, develop an evidence-informed clinical implications statement. The clinical implications statement was shared with the Ontario Health (Cancer Care Ontario) Acute Leukemia Advisory Committee and the Transplant and Cellular Therapy Advisory Committee which include clinical and administrative representatives from across Ontario.. Committee members were given the opportunity to discuss and revise the statement.

Results

The search identified 182 articles and an additional 30 references through the grey literature searches. Five studies were identified investigating the effect of blinatumomab prior to anti-CD19 CAR T-cell therapy in adult patients with ALL (**Figure 1**).

Figure 1: PRISMA diagram



The identified studies included various methodologies, including clinical trials(1,2), retrospective cohort (abstract only)(3), case series(4), and a case study(5).

Clinical Implications

At this time, there is no definitive evidence that administering a full course of blinatumomab prior to CAR T-cell therapy provides additional clinical benefit for patients with acute lymphoblastic leukemia (ALL). Likewise, current data do not demonstrate a detrimental impact of blinatumomab on the efficacy of subsequent CAR T-cell therapy. If a patient receives blinatumomab and relapses or is refractory, CD19 positivity must be reconfirmed before proceeding with CAR T-cell therapy enrolment.

Blinatumomab may be considered as a bridging therapy prior to CAR T-cell infusion. However, for this purpose, no more than two cycles should typically be administered. With regard to Ontario funding eligibility, if additional cycles are deemed necessary, the rationale must be clearly documented and submitted alongside the CAR T-cell enrollment form. Acceptable reasons may include, but are not limited to, manufacturing delays in CAR T-cell production.

Table 2: Evidence table

Author, (year) Country	Study Design	Population	Outcome Measures	Results
Shah B.D (2021) (1) United States, Canada, Europe (multi-centre) Trial ID: NCT02614066	Phase 2, single arm, open-label	Adult r/r B-ALL N=55 CAR T tx: KTE-X19, Brexucabtagene Autoleucel (Tecartus) (Characteristics not dichotomized) Age median (IQR): 40 (28,52) Female: 33 (60%) ECOG of 1: 39 (71%) Ph+: 15 (27%) CNS-1 at baseline: 55 (100%) Previous inotuzumab ozogamicin: 12 (22%) Previous Allo SCT: 23 (42%) Prior blina: n=25 No prior blina: n=30	Overall Complete remission (CR)/ CR with incomplete hematologic recovery (CRi)	**CR/CRi:** n, (%) [95% CI] Prior blina: 15 (60%) [39-79] No prior blina: 24 (80%) [61-92] <Forest plot line of no effect set at 70%>
Park 2018 (2) United States	Phase 1, single arm	Adult r/r B-ALL	Complete remission (CR)	**CR:**

Author, (year) Country	Study Design	Population	Outcome Measures	Results
(single-centre) Trial ID: NCT01044069		N=53 (n=13 previously treated with blinatumomab) CAR T tx: study manufactured product/ not commercially available. All pts: Age median (range): 44 (23-74) Ph+: 16 (30%)		All pts: 44 (83%) [includes blina pts] Blina pts alone: 9 (69%)
Gupta V. (2023) (3) United States (multi-centre)	Retrospective cohort (abstract only)	Adult r/r B-ALL N=152 CAR T tx: Brexucabtagene Autoleucel (Tecartus) **Blinatumomab responders (B-R)** achieving CR/CRi to any number of cycles (median cycles 2 (range 1-12): n=62 Age [median (IQR)]: 51 (37, 62) Female: 31 (50%) Pre-apheresis disease burden: Active disease: 25 (40%) CR/MRD+: 21 (34%) CR/MRD-: 9 (15%) CR unknown MRD: 2 (3%) Blina response, pre-apheresis: No response/active disease: 0 CR/MRD+: 19 (31%) CR/MRD-: 39(63%)	CR/CRi at 28 days post CAR T CD19- relapse status (yes/no) Death in remission (Yes/No) 1-year duration of response (DOR): % survived) 1-year progression-free survival (PFS): % survived 1-year overall survival (OS): % survived	**Day 28 post CAR T response:** **No Response:** B-R: 6 (10%) B-NR: 1 (4%) Blina-naïve: 6 (9%) **CR/MRD+:** B-R: 8 (13%) B-NR: 5 (19%) Blina-naïve: 5 (8%) **CR/MRD-:** B-R: 40 (65%) B-NR: 16 (62%) Blina-naïve: 43 (67%) **CR/unknown MRD:** B-R: 1 (2%) B-NR: 1 (4%) Blina-naïve: 2 (3%) **CR (all MRD status' combined):** B-R: 49/62 (79%) B-NR: 22/26 (85%)

Author, (year) Country	Study Design	Population	Outcome Measures	Results
		CR achieved by morphology without MRD testing: 3 (5%) **Blinatumomab non-responders (B-NR)**: achieving CR/CRi to any number of cycles (median cycles 1 (range 1-4): n=26 Age: 40 (29, 62) Female: 8 (31%) Pre-apheresis disease burden: Active disease: 16 (62%) CR/MRD+: 3 (12%) CR/MRD-: 3 (12%) CR unknown MRD: 0 Blina response, pre-apheresis: No response/active disease: 26 (100%) CR/MRD+: 0 CR/MRD-: 0 CR achieved by morphology without MRD testing: 0 **Blinatumomab naïve (Blina-naïve):** n=64 Age: 40 (28, 60) Female: 26 (41%) Active disease: 38 (59%) CR/MRD+: 11 (17%) CR/MRD-: 10 (16%) CR unknown MRD: 1 (2%)		Blina-naïve: 50/64 (78%) **Unknown:** B-R: 7 (11%) B-NR: 3 (12%) Blina-naïve: 8 (13%) **CD19- relapse status:** B-R: Yes: 8 (18%); No: 32 (73%); Unknown: 4 (9%) B-NR: Yes: 4 (29%); No: 6 (43%); Unknown: 4 (29%) Blina-naïve: Yes: 3 (8%); No: 30 (83%); Unknown: 3 (8%) **Death in remission:** B-R: 10/62 (16%) B-NR: 4/26 (15%) Blina-naïve: 8/64 (13%) **1-year DOR:** B-R: (49%) B-NR: (50%) Blina-naïve: (77%) **1-year PFS:** B-R: (37%) B-NR: (30%) Blina-naïve: (60%) **1-year OS:** B-R: (65%) B-NR: (32%) Blina-naïve: (71%)

Author, (year) Country	Study Design	Population	Outcome Measures	Results
Danylesko I. (2020) (4) Israel (single centre) Trial ID: NCT02772198	Case series	Adult B-ALL N=5 CAR T tx: study manufactured product/ not commercially available. **Pt 1:** 25 y/o, normal karyotype, active disease, prior mismatched allo-unrelated [received inotuzumab ozogamicin] **Pt 2:** 37 y/o, normal karyotype, MRD+, prior allo-unrelated [received both blinatumomab and inotuzumab ozogamicin] **Pt 3:** 59 y/o, T9; 11, 20q, active disease [received blinatumomab] **Pt 4:** 48 y/o, normal karyotype, active disease, prior allo-related [received blinatumomab] **Pt 5:** 27 y/o, Ph+, MRD+ [received inotuzumab ozogamicin]	Complete remission (CR) (yes/no; MRD +/-) Cytokine release syndrome (CRS) level (I-III) CNS toxicity (none, I-IV) Status at last f/u	**Response 28 days after CAR T:** Pt 1: CR MRD+ Pt 2: CR MRD- Pt 3: Not reached Pt 4: CR MRD+ Pt 5: CR MRD+ **CRS level:** Pt 1: I Pt 2: I Pt 3: III Pt 4: I Pt 5: I **CNS toxicity:** Pt 1: None Pt 2: None Pt 3: III Pt 4: None Pt 5: None **Status at last f/u:** Pt 1: Alive/ active disease Pt 2: Alive/ CR Pt 3: Dead/ treatment-related Pt 4: Alive/ CR Pt 5: Alive/ CR
Myers R.M (2023) (5) United States	Case Study	r/r B-ALL CAR T Tx: Tisagenlecleucel (Kymriah) Age: 19 y/o Male Normal cytogenetics Persistent CD19+ disease	CR/CRi at 28 days post CAR T Cytokine release syndrome (CRS) level (I-III)	**Day 28 post CAR T response:** MRD- "remains low-level positive at day +60 with concurrent loss of BCA as the absolute CD19+ count rises to 75/µL." **CRS:** II without ICANS

References

1. Shah BD, Ghobadi A, Oluwole OO, Logan AC, Boissel N, Cassaday RD, et al. KTE-X19 for relapsed or refractory adult B-cell acute lymphoblastic leukaemia: phase 2 results of the single-arm, open-label, multicentre ZUMA-3 study. The Lancet [Internet]. 2021;398(10299):491–502. Available from: http://www.journals.elsevier.com/the-lancet/
2. Park JH, Rivière I, Gonen M, Wang X, Sénéchal B, Curran KJ, et al. Long-Term Follow-up of CD19 CAR Therapy in Acute Lymphoblastic Leukemia. New England Journal of Medicine [Internet]. 2018;378(5):449–59. Available from: https://www.nejm.org/doi/full/10.1056/NEJMoa1709919
3. Gupta VK, Roloff GW, Muffly LS, Aldoss I, Kopmar NE, Lin C, et al. Impact of Prior Response to Blinatumomab on Outcomes of Brexucabtagene Autoleucel (Brexu-cel) in Adult Patients with Relapsed or Refractory (r/r) B-Cell Acute Lymphoblastic Leukemia (B-ALL): Results from the Real-World Outcomes Collaborative of CAR-T in Adult ALL (ROCCA). Blood [Internet]. 2023;142(Supplement 1):2119. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emexa&NEWS=N&AN=2028732880
4. Danylesko I, Chowers G, Shouval R, Besser MJ, Jacoby E, Shimoni A, et al. Treatment with anti CD19 chimeric antigen receptor T cells after antibody-based immunotherapy in adults with acute lymphoblastic leukemia. Curr Res Transl Med [Internet]. 2020;68(1):17–22. Available from: http://www.journals.elsevier.com/current-research-in-translational-medicine
5. Myers RM, Shah NN, Pulsipher MA. How I use risk factors for success or failure of CD19 CAR T cells to guide management of children and AYA with B-cell ALL. Blood [Internet]. 2023;141(11):1251–64. Available from: https://doi.org/10.1182/blood.2022016937

Appendix A

Table A1: Evidence Review Working Group

Name	Affiliations
Alejandro Garcia-Horton	Hematologist, Hamilton Health Sciences Centre Committee member, Acute Leukemia Advisory Committee
Andre Schuh	Hematologist, University Hospital Network – Princess Margaret Hospital
Chris Bredeson	Hematologist, The Ottawa Hospital Committee co-chair, Acute Leukemia Advisory Committee Committee co-chair, Transplant and Cellular Therapy Advisory Committee Provincial Head, Complex Malignant Hematology, Ontario Health (Cancer Care Ontario)
Rena Buckstein	Hematologist, Sunnybrook Health Sciences Centre Committee member, Acute Leukemia Advisory Committee
Tom Kouroukis	Hematologist, Hamilton Health Sciences Centre Committee member, Acute Leukemia Advisory Committee Committee member, Transplant and Cellular Therapy Advisory Committee Clinical Lead, Quality Care and Access, Complex Malignant Hematology and PDRP Hematology Cancer Lead, Ontario Health (Cancer Care Ontario)
Cassandra McKay	Manager, Specialized Services Oversight, Ontario Health (Cancer Care Ontario)
Lisa Milgram	Manager, Provincial Drug Reimbursement Programs, Ontario Health (Cancer Care Ontario)
Arthur Manzon	Senior Advisor, Out of Country Program, Ontario Health (Cancer Care Ontario)
Leslie Verville	Specialist, Specialized Services Oversight, Ontario Health (Cancer Care Ontario)