SAFETY AND FEASIBILITY OF BLINATUMOMAB AS FRONTLINE THERAPY FOR PEDIATRIC PATIENTS WITH B-ACUTE LYMPHOBLASTIC LEUKEMIA AND LYMPHOMA: ST. JUDE TOTAL THERAPY STUDY XVII

Caitlyn Duffy[1], Elizabeth R Dang[1], Yinmei Zhou[1], Jessica Bell[2], Nickhill H Bhakta[1], Meret Henry[3], Kenneth M Heym[4], Sima Jeha[1], Noman J Lacayo[5], Seth E Karol[1], Seong L Khaw[6], Raul C Ribeiro[1], Deborah E Schiff[7], Charles G Mullighan[1], Jun J Yang[1], Cheng Cheng[1], Ching-Hon Pui[1], Hiroto Inaba[1]

[1]St. Jude Children's Research Hospital, Memphis, TN, USA, [2]Novant Health Hemby Children's Hospital, Charlotte, NC, USA, [3]Children's Hospital of Michigan, Detroit, MI, USA, [4]Cook Children's Healthcare System, Fort Worth, TX, USA, [5]Stanford University, Stanford, CA, USA, [6]Royal Children's Hospital, Melbourne, Australia, [7]Rady Children's Hospital, San Diego, CA, USA

INTRODUCTION

- St. Jude Total Therapy Studies XV and XVI demonstrated that, for children with acute lymphoblastic leukemia (ALL), minimal residual disease (MRD) ≥ 0.01% at the end of induction (EOI) and/or high-risk (HR) genetic subtypes were associated with poorer survival.
- TOTXVII aimed to improve cure and quality of life by employing precision medicine guided by flow cytometry-based MRD detection and next-generation sequencing-based genetic characterization in children with ALL and lymphoblastic lymphoma (LLy).
- Blinatumomab, a bispecific T-cell engager, is approved for adult and pediatric patients with B-ALL. Like other immunotherapies, blinatumomab is associated with an increased risk of cytokine release syndrome (CRS) and neurotoxicity and is complex to administer due to continuous 28-day infusion.
- Further work is needed to optimize patient selection and characterize how practical challenges impact patient subgroups.

AIM

- This study evaluated the safety and feasibility of blinatumomab during treatment in pediatric patients with B-ALL or B-LLy with high-risk features and those who were intolerant of conventional chemotherapy.
- ClinicalTrials.gov ID NCT03117751

RESULTS

- 621 patients (612 B-ALL, 9 B-LIy) were enrolled in TOTXVII, 147 received blinatumomab (116 Protocol defined; 31 Interim Therapy)
- 279 cycles were observed, 57 interruptions occurred in 46 cycles (16.5% cycles affected)
  - 68.4% (n=39) of interruptions ≥4 hours requiring readmission
  - Interruptions attributed to AEs (n=25, 43.9%), equipment issue (n=21, 36.8%), physician or family preference (n=11, 19.3%)
  - 33.3% (n=19) of interruptions resulted in permanent discontinuation (neurotoxicity responsible for 31.6%, n=6)

Table 1. TOTXVII blinatumomab patient demographics

Characteristic	Protocol Defined, n=116 (%)	Interim Therapy, n=31 (%)
Age at diagnosis, years		
1-10	67 (57.8)	19 (61.3)
>10	49 (42.2)	12 (38.7)
Sex		
Male	65 (56.0)	18 (58.1)
Female	51 (44.0)	13 (41.9)
Race		
White	73 (62.9)	25 (80.1)
Black	12 (10.3)	1 (3.2)
Others	31 (26.7)	5 (16.1)
Diagnosis		
ALL	113 (97.4)	31 (100.0)
LLy	3 (2.6)	0 (0)
Leukocyte count, cells/μL		
<10,000	53 (45.7)	10 (32.3)
10,000 to <50,000	29 (25.0)	10 (32.3)
50,000 to <100,000	16 (13.8)	6 (19.4)
≥ 100,000	14 (12.1)	5 (16.1)
Unknown	4 (3.4)	0 (0)
CNS Status		
CNS1	80 (69.0)	21 (67.7)
CNS2	18 (15.5)	6 (19.4)
CNS3	8 (6.9)	1 (3.2)
Traumatic with blasts	7 (6.0)	3 (9.7)
Unknown	3 (2.6)	0 (0)
Down Syndrome		
Present	7 (6.0)	3 (9.7)
Absent	109 (94.0)	28 (90.3)
MRD at end of induction, % (ALL only)		
<0.01	79 (68.1)	28 (90.3)
0.01-0.99	33 (28.4)	1 (3.2)
1-4.99	0 (0)	1 (3.2)
≥ 5	0 (0)	1 (3.2)
Unknown	1 (0.9)	0 (0)

Figure 1. TOTXVII Blinatumomab Indications

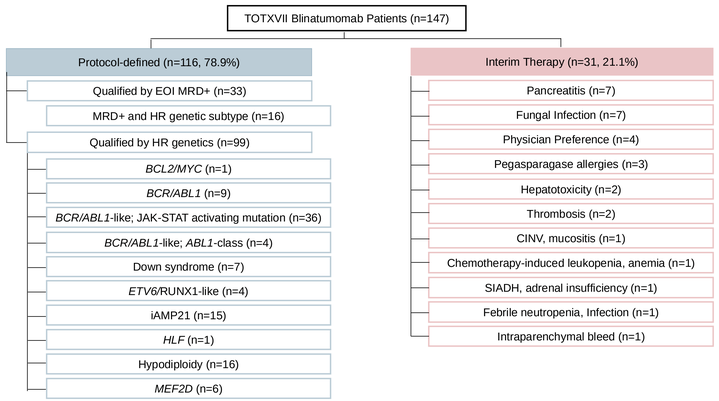

Table 2. Feasibility: Blinatumomab infusion interruptions and discontinuations

	Protocol Defined, n=116		Interim Therapy, n=31	
	Cycle 1	Cycle 2	Cycle 1	Cycle 2
Total interruptions	**23**	**20**	**7**	**7**
Patients with interruptions	14	20	7	5
Discontinuations	4	9	2	4
Interruption duration				
<4 hours	11	5	1	1
AEs	Seizure (1)	CRS (1)	Fungal Infection (1)	Neurotoxicity (1)
Other	Equipment (9) Physician preference (1)	Equipment (4)	-	-
≥4 hours (interruption only)	8	6	4	3
AEs	CRS (2), Neurotoxicity (1), Seizure (1), ALT elevation (1)	CRS (1)	CRS (1), Seizure (1), Other (1)	Neurotoxicity (2), CRS (1)
Other	Equipment (2) Family preference (1)	Equipment (4) Family preference (1)	Physician Preference (1)	
Prolonged interruptions resulting in discontinuation	4	9	2	4
AEs	Seizure (2), Neurotoxicity (1), Allergic reaction (1)	Neurotoxicity (2), Other (1), ALT elevation (1)	Cardiac Event (1)	Pancreatitis (1), Cardiac event (1), Neutropenia (1) Neurotoxicity (1),
Other	-	Physician preference (2), Family Preference (1), Equipment (1) Disease progression (1)	Family preference (1)	-

3 patients with interruptions during cycle 1 and cycle 2, counted in both categories. Other = decompensation NOS (n=1), possible infection (n=1), rash (n=1)

Table 3. Safety: Adverse events during blinatumomab infusion

	Protocol Defined (n=116)		Interim Therapy (n=31)	
	Cycle 1	Cycle 2	Cycle 1	Cycle 2
Cytokine Release Syndrome (CRS):				
Median day of onset	2	1.5	N/A	2
Any grade	8	2	0	1
≥3 grade	2	1	0	0
Neurotoxicity (including seizure)				
Median day of onset	2.5	N/A	8	7.5
Any grade	4	0	1	2
≥3 grade	1	0	0	2
Seizure				
Median day of onset	2	N/A	8	N/A
Any grade	3	0	1	0
≥3 grade	0	0	0	0
Infection				
Any grade	14	17	1	2
≥3 grade	7	7	1	2
Upper Respiratory Infection	10	11	0	1
COVID-19	4	2	0	0
Rhinovirus A	2	3	0	0
Respiratory Syncytial Virus	2	1	0	0
Metapneumovirus	1	0	0	1
Influenza A	0	1	0	0
Influenza B	0	1	0	0
Parainfluenza Virus	0	2	0	0
Unknown	1	1	0	0
Bacteremia (*S. epidermidis*)	1	0	0	0
Enterocolitis	1	1	0	0
Ear Infection	0	1	0	1
Skin Infection/Paronychia	1	4	0	0
Viral Exanthem	1	0	0	0
Catheter Related Infection	0	0	1	0
Fever				
Any grade	19	11	1	1
≥3 grade	19	10	1	1
Febrile Neutropenia				
Any grade	6	1	0	0
≥3 grade	6	1	0	0
Increased Alanine Aminotransferase				
Any grade	6	3	0	0
≥3 grade	6	3	0	0
Hyperglycemia				
Any grade	5	1	0	0
≥3 grade	5	1	0	0
Hypokalemia				
Any grade	3	2	0	0
≥3 grade	3	2	0	0
Pancreatitis				
Any grade	0	0	0	1
≥3 grade	0	0	0	1
Acute Kidney Injury				
Any grade	0	1	0	0
≥3 grade	0	0	0	0
Thrombus				
Any grade	1	0	0	0
≥3 grade	1	0	0	0

METHODS

- Between 2017-2023, children aged 1–18 years at diagnosis received up to 2 consecutive cycles of blinatumomab in TOTXVII.
- **Indications**
  1. Protocol-defined patients with HR features:
     - EOI MRD of 0.01%–1.00%
       and/or
     - HR genetic subtypes (*BCR::ABL1*, *BCR::ABL*-like [with JAK–STAT activating mutations or *ABL1*-class fusions], iAMP21, hypodiploidy, *MEF2D* fusions, *ETV6::RUNX1*-like, *TCF3::HLF*, *BCL2/MYC*) or Down syndrome (DS)
  2. Interim therapy: patients intolerant of conventional chemotherapy
- **Feasibility** assessed by evaluation of cycle interruptions and discontinuations during blinatumomab treatment
  - Interruptions classified by frequency, indication, and duration (<4 hours or ≥4 hours), and if they resulted in permanent discontinuation
  - Interruptions lasting ≥4 hours required readmission for reinitiation
  - Patients who received 1 cycle of blinatumomab but did not receive a second due to toxicity or other unanticipated reason were considered discontinued.
- **Safety** assessed by evaluating AE frequency and severity based on CTCAE version 4.0.

CONCLUSIONS

- Blinatumomab is feasible and well-tolerated as part of frontline therapy for pediatric patients with B-ALL/LLy and high-risk features (EOI MRD 0.01%-<1.00% and/or genetic subtype) or are intolerant of conventional therapy with expected AE profiles. Most AEs observed in protocol-defined patients.
- Tolerability may be improved with efforts to prevent short and long-term interruptions, especially due to non-clinical causes such as equipment issues.
- Further analysis will (1) compare AEs in TOTXVII patients receiving blinatumomab to those in TOTXVI who received conventional chemotherapy and (2) evaluate survival outcomes associated with blinatumomab in this patient population.

ACKNOWLEDGEMENTS

This study was supported by the Cancer Center Support (CORE) Grant (CA021765) from the National Cancer Institute, the American Lebanese Syrian Associated Charities (ALSAC), and Amgen.

CONTACT

Caitlyn Duffy: caitlyn.duffy@stjude.org