

Combination low-intensity chemotherapy plus inotuzumab ozogamicin, blinatumomab and rituximab for pediatric patients with relapsed/refractory B-cell acute lymphoblastic leukemia

Authors

Amber Gibson,¹ Cesar Nunez,¹ Lindsay Robusto,² Brianna Kammerer,¹ Miriam Garcia,¹ Michael Roth,¹ Rachna Sheth,¹ Priti Tewari,¹ Aline Hittle,¹ Laurie Toepfer,¹ Romeo Torres,¹ Nicholas J. Short,³ Elias Jabbour,³ Nitin Jain,³ Branko Cuglievan¹ and David McCall¹

Correspondence:

A. GIBSON - algibson2@mdanderson.org

<https://doi.org/10.3324/haematol.2023.284950>

¹Department of Pediatrics; ²Department of Pharmacy and ³Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Supplementary Table 1: Mini-Hyper CVD Treatment Schema

Mini-hCVD (odd cycles)

Cyclophosphamide	150 mg/m ² IV every 12 hours days 1-3 (6 total doses)
Dexamethasone	10 mg/m ² IV every 12 hours (max 20 mg/day) days 1-4 and 11-14
Vincristine	1.5 mg/m ² (max 2 mg/dose) IV days 1 and 8
Peg filgrastim	0.1 mg/kg (max 6 mg) subcutaneous day 4
Intrathecal therapy	Dosing below. Days 1 and 8

Methotrexate/Cytarabine (even cycles)

Methotrexate	250 mg/m ² CIV over 24 hours (50 mg/m ² over 2 hours then 200 mg/m ² over 22 hours) day 1
Cytarabine^a	0.5 grams/m ² IV every 12 hours days 2 and 3 (4 total doses)
Peg filgrastim	0.1 mg/kg (max 6 mg) subcutaneous day 5
Intrathecal therapy	Dosing below. Days 1 and 8

Immunotherapy^b

Inotuzumab ozogamicin	<u>Cycle 1:</u> 0.6 mg/m ² IV day 2 and 0.3 mg/m ² days 8 and 15 <u>Cycle 2 and after:</u> 0.3 mg/m ² IV days 2 and 8
Blinatumomab	<u>Cycle 1:</u> 5 mcg/m ² /day (max 9 mcg/day) CIV days 14-17 then 15 mcg/m ² /day (max 28 mcg/day) CIV days 18-29 <u>Cycle 2 and after:</u> 15 mcg/m ² /day (max 28 mcg/day) CIV days 4-28
Rituximab	<u>All Cycles:</u> 375 mg/m ² IV days 2 and 8

For Leukemia CNS1 or 2: The intrathecal therapies will consist of below:

Methotrexate (MTX)	Age (yrs) 1-1.99	Dose MTX:8mg,
	2-2.99	MTX: 10mg
	3-8.99	MTX: 12 mg
	≥9	MTX: 15 mg

For Leukemia CNS 3: The intrathecal therapies will consist of triple therapies as listed below:

Methotrexate (MTX) Hydrocortisone (HC) Cytarabine (ARAC)	Age (yrs) 1-1.99	Dose MTX:8mg, HC: 8mg, ARAC: 16mg
	2-2.99	MTX: 10mg HC: 10 mg ARAC: 20 mg
	3-8.99	MTX: 12 mg HC: 12 mg ARAC: 24 mg
	≥9	MTX: 15 mg HC: 15 mg ARAC: 30 mg

Supplemental Table 1: Abbreviations: mini-hCVD, hyper-fractionated cyclophosphamide, vincristine, and dexamethasone; IV, intravenous; subcutaneous, subcutaneously; CIV, continuous intravenous infusion.

Supportive care: ursodiol 5 mg/kg orally twice daily starting day 1 if inotuzumab administered; urine alkalinization for methotrexate with continuous IV sodium acetate at 2-times maintenance fluid rate to maintain urine pH >7. Leucovorin rescue began 12 hours after end of methotrexate infusion 15 mg/m² IV every 6 hours until methotrexate level <0.01 mcmol/L. Methotrexate levels obtained at end of infusion and every 24 hours thereafter until level <0.01 mcmol/L.

^a Cytarabine delayed until methotrexate level less than 20 mcmol/L if necessary

^b Immunotherapy administered based on patient expression of CD19 (blinatumomab), CD20 (rituximab), and/or CD22 (inotuzumab ozogamicin)

Supplementary Table 2: Adverse Events per CTCAE v5

Adverse Event, N (%)	Grade 2	Grade 3	Grade 4
VOD/SOS during subsequent HSCT	0	1 (10)	1 (10)
Cytokine release syndrome	0	0	0
Febrile neutropenia	0	3 (30)	0
Sepsis	0	1 (10)	0
INR increase	2 (20)	0	0
ALT increase	2 (20)	1 (10)	0
Hyperglycemia	1 (10)	1 (10)	1 (10)
Neuropathy	1 (10)	0	0
Decreased Fibrinogen	1 (10)	0	0
Constipation	1 (10)	0	0

Supplemental Table 2: Abbreviations: INR- International normalized ratio. ALT- Alanine transaminase. VOD- Veno-Occlusive disease. SOS- Sinusoidal obstructive syndrome. HSCT- hematopoietic stem cell transplant.