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POSTER ABSTRACTS

614.ACUTE LYMPHOBLASTIC LEUKEMIAS: THERAPIES, EXCLUDING TRANSPLANTATION AND CELLULAR IMMUNOTHERAPIES

"Dose-Dense" Mini-Hyper-CVD, Inotuzumab Ozogamicin and Blinatumomab Achieves High Rates of Rapid MRD-Negativity in Patients with Philadelphia Chromosome-Negative B-Cell Acute Lymphoblastic Leukemia: A Retrospective Analysis

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Background: Mini-hyper-CVD plus inotuzumab ozogamicin (InO) followed by sequential blinatumomab (Blina) is effective in both older adults with newly diagnosed B-cell ALL and in relapsed/refractory disease. We hypothesized that concomitant administration of these agents in a "dose-dense" (DD) fashion would also be safe and effective in B-cell acute lymphoblastic leukemia (ALL), leading to rapid measurable residual disease (MRD) negativity.
Methods: This is a retrospective analysis of patients (pts) with B-cell ALL who received DD mini-hyper-CVD + InO + Blina outside of a clinical trial. All pts received mini-hyper-CVD alternating with mini-methotrexate and cytarabine in combination with InO. To be evaluable for this analysis, Blina must have started prior to day 21 of the first cycle of therapy. Pts were included if they received this regimen for 1.) frontline induction, 2.) treatment of MRD-positive remission, or 3.) salvage therapy for relapsed/refractory (R/R) disease.
Results: Between 7/2020 and 1/2023, 21 eligible pts were treated **(Table 1)**. The median age was 48 years (range, 6-74 years); 3 pts (all in the R/R cohort) were <18 years old. 9 pts (43%) were treated as frontline therapy, 4 (19%) for treatment of MRD (3 for flow-positive MRD and 1 for persistent FISH for t[4;11]), and 8 (38%) for R/R disease. In the MRD cohort, 3 pts were in first CR and 1 was in second CR; 1 pt received prior InO and 1 had prior allogeneic stem cell transplant (alloSCT). In the R/R cohort, pts were heavily pretreated, with a median number of prior therapies of 3 (range, 1-7); 2 pts received prior InO, 3 pts received prior Blina, 3 pts had undergone prior allo SCT, and 3 pts had received prior chimeric antigen receptor T-cell (CAR-T cell) therapy. Three pts (all in the R/R cohort) had extramedullary (EM) disease, 2 outside of the CNS without marrow disease and 1 with CNS disease and bone marrow MRD by flow.
Pts received a median of 2 cycles (range, 1-5) of a dose-dense regimen. All pts received 0.9 mg/m ^{2} InO in cycle 1, except for 1 pt in the R/R cohort who received 0.6 mg/m ^{2} due to myelosuppression with prior InO. Themedian cumulative dose of InO was 1.2 mg/m ^{2} (range, 0.6-2.7 mg/m ^{2}). Blina was started on a median of day 4 (range, day 4-17) of the first cycle of chemotherapy. Blina was started by day 7 in 16 pts (76%).
In the frontline cohort, all pts (100%) achieved CR/CRi (CR in 8 pt and CRi in 1 pt), all after cycle 1 (**Table 2)**. All pts in the frontline cohort achieved flow MRD negativity. 7 pts were evaluable for bone marrow next generation sequencing (NGS) MRD (sensitivity 10 $^{-6}$). Of these, 4/6 (67%) achieved NGS MRD negativity after cycle 1, and all 7 evaluable pts (100%) achieved NGS MRD negativity. In the MRD cohort, all 3 flow-positive pts became flow MRD negative after cycle 1; the pt with positive FISH for t(4;11) became FISH-negative after cycle 2. 3 of the 4 pts in the MRD cohort (75%) became NGS MRD negative. Overall, 5 of the 8 pts (63%) in the R/R cohort achieved CR/CRi. Among 5 evaluable pts in the R/R cohort with marrow disease (including the pt with CNS disease and MRD-positive marrow), all achieved flow MRD negativity after cycle 1. Overall, 7 pts (33%) underwent consolidative alloSCT (2 in the MRD cohort and 5 in the R/R cohort), and 1 pt in the MRD cohort underwent consolidative CAR-T cell therapy.

The treatment regimen was well tolerated. No patients developed sinusoidal obstruction syndrome/veno-occlusive disease. One pt had grade 1 CRS, and 2 pts had grade 1 tremor.
With a median follow-up of 13.4 months (range, 0.5-20.6 months), 6 pts (29%) have died (1 in the frontline cohort, 1 in the MRD cohort and 4 in the R/R cohort). 3 deaths were due to complications of alloSCT, 2 were due to sepsis (1 in the setting of refractory leukemia and 1 during MRD-negative CR), and 1 from unknown cause. Among 18 responding pts, only 1 pt relapsed; the pt with MRD-positive t(4;11) by FISH relapsed 4.5 months after alloSCT. The median OS for the R/R cohort was 5.8 months and was not reached for the frontline or MRD cohorts. The 1-year OS rate for the frontline + MRD cohort was 83%.
Conclusion: Dose-dense mini-hyper-CVD in combination with InO and Blina achieves rapid MRD-negative remissions in patients with B-cell ALL. All responding patients achieved flow MRD negativity after 1 cycle of therapy, with the majority also achieving NGS MRD negativity. This regimen is now being prospectively evaluated in an ongoing clinical trial in pts with R/R B-cell ALL and in older adults with newly diagnosed B-cell ALL.

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Table 1. Baseline Characteristics.

Characteristic N (%); median [range]	Frontline (N=9)	Consolidation (N=4)	Relapsed/Refractory (N=8)
Age (years)	45 [20-74]	30 [19-42]	24 [6-61]
Cytogenetics			
Diploid	4 (44)	2 (50)	3 (38)
Complex	0	0	2 (25)
High hyperdiploid	1 (11)	0	0
Low hypodiploid	2 (22)	0	0
t(4;11)	0	1 (25)	0
Miscellaneous	2 (22)	1 (25)	2 (25)
Inadequate sample	0	0	1 (13)
Bone marrow blasts (%)	83 [33-95]	----	62 [4-97]
Ph-like ALL	3 (33)	1 (25)	1 (13)
***TP53* mutation**	2 (22)	0	3 (38)
Extramedullary disease	0	0	3 (38)
# of prior therapies	----	----	3 [1-7]
Prior Inotuzumab	----	1 (25)	2 (25)
Prior Blinatumomab	----	0	3 (38)
Prior alloSCT	----	1 (25)	3 (38)
Prior CAR-T therapy	----	0	3 (38)

Table 2. Treatment Response and Disposition.

Category N (%)	Frontline (N=9)	Consolidation (N=4)	Relapsed/Refractory (N=8)
CR/CRi rate#	9 (100)	-----	5 (63)
MRD negativity by flow*			
After cycle 1	9 (100)	3/3 (100)	5/5 (100)
Overall	9 (100)	3/3 (100)	5/5 (100)
MRD negativity by NGS			
After cycle 1	4/6 (67)	2 (50)	----
At any time	7/7 (100)	3 (75)	
CAR-T consolidation	0	1 (25)	0
alloSCT consolidation	0	2 (50)	5 (63)

Including only patients with baseline morphological marrow or extramedullary disease

* Including only patients with baseline flow-detectable marrow disease

Figure 1

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