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POSTER ABSTRACTS

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

A Phase II Study of Low-Intensity Chemotherapy (Mini-Hyper-CVD) and Ponatinib Followed By Blinatumomab and Ponatinib in Patients with Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia

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Background

Patients with Philadelphia chromosome (Ph)-positive B-cell acute lymphoblastic leukemia (ALL) treated with Hyper-CVAD and ponatinib achieve deep responses and long-term overall survival (OS). We aim to investigate if a reduced intensity regimen of mini-Hyper-CVD (mini-HCVD) with sequential blinatumomab (blina) in combination with ponatinib may further improve outcomes while mitigating the toxicity of intensive chemotherapy and the need for hematopoietic stem cell transplantation (HSCT).

Methods

Patients age ≥18 years with newly diagnosed (ND) or relapsed/refractory (R/R) Ph-positive ALL, or chronic myeloid leukemia in lymphoid blast phase (CML-LBP) were eligible. Other inclusion criteria included adequate liver, renal and cardiac function, and ECOG performance status ≤2. Patients with baseline central nervous system (CNS) involvement were not excluded. All patients had *BCR::ABL1* transcripts and fluorescence *in situ* hybridization (FISH) for t(9;22) done at baseline. Morphological analysis of FISH patterns was performed in ND patients to identify if the *BCR::ABL1* signal was observed in myeloid cells (e.g., segmented neutrophils). Four cycles (C) of mini-HCVD alternating with methotrexate (MTX) + cytarabine were followed by blina 28µg/d given for four weeks every six weeks during C5-8. Patients received ponatinib 30mg daily initially, with a dose reduction to 15mg daily once in complete molecular remission (CMR). CMR was defined as undetectable *BCR::ABL1* with an assay sensitivity of 0.01%. Rituximab was given for CD20-positive disease. Maintenance ponatinib, vincristine and prednisone for 15 cycles with blina + ponatinib every three cycles was given, followed by ponatinib for at least five years. All patients without CNS disease received 12 intrathecal injections of MTX or cytarabine.

Results

20 patients (12 ND, 4 R/R, 4 CML-LBP) were treated between November 2019 and May 2023. Baseline characteristics are shown in Table 1. One patient with CML-LBP had received prior dasatinib while in chronic phase. The predominant *BCR::ABL1* transcript was p190 in 7 (58%) ND patients. All patients achieved a complete remission (CR). Among patients in the ND, R/R, and CML-LBP cohorts, CMR was achieved in 10/12 (83%), 3/4 (75%), and 4/4 (100%) patients, respectively. In the ND cohort, six (50%) patients achieved CMR after C1 and eight (67%) after C3. Five (42%) ND patients had documented BCR::ABL1 signal in myeloid cells by FISH. Four of them achieved CMR, after C1, C3, C4 and C3 maintenance respectively.

With a median follow-up of 25 months (range, 2-42), the 2-year continuous remission duration (CRD) and OS rates were 93% and 83% for the entire cohort (Figure 1), and 90% and 82% in the ND cohort, respectively. In the ND cohort, one (8%) patient had isolated CNS relapse (during C4 of maintenance with blina and ponatinib), three (25%) patients died (two in CR due to COVID-19 and one of HSCT complications), and eight (67%) patients are in remission without HSCT. No patients relapsed in the R/R cohort; one patient underwent HSCT, one patient died in CR from MTX-associated disseminated necrotizing leukoencephalopathy, and two patients are in remission without HSCT. None of the CML-LBP relapsed; one patient underwent HSCT in CR.

Ponatinib dose was reduced in two patients prior to obtaining CMR (one had pancreatitis, one had cardiomyopathy). One patient switched from ponatinib to dasatinib due to a pulmonary embolism in C2. No patients required dose modification of blina. The 60-day mortality rate was 0%.

Conclusion

In patients with Ph-positive ALL, the combination of mini-HCVD and ponatinib followed by sequential blina and ponatinib yielded excellent outcomes with durable remissions. The toxicity profile was favorable and HSCT was avoided in most patients with ND disease. Longer follow-up is needed to confirm the durability of responses.

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Table 1: Baseline patient characteristics

Characteristic N (%) / median [range]	Total N = 20	ND N = 12	R/R N = 4	CML-LBP N= 4
Age	41 [25-61]	41 [25-59]	43 [31-49]	41 [33-61]
Female Gender	12 (60)	9 (75)	1 (25)	2 (50)
Performance Status <2	20 (100)	12 (100)	4 (100)	4 (100)
WBC ($x10^9$/L)	21.8 [1.8-266.5]	21.0 [1.8-266.5]	5.2 [3.6-6.7]	52.0 [14.4-146]
CNS involvement	1 (5)	0	0	1 (25)
CD20 expression ≥20%	5 (25)	5 (42)	0	0
BCR::ABL1 transcript				
p190	7/19 (37)	7 (58)	0	0
p210	12/19 (63)	5 (42)	3/3 (100)	4 (100)
Frontline	16 (80)	12 (100)	0	4 (100)
Salvage 1	3 (15)	0	3 (75)	0
Salvage 2+	1 (5)	0	1 (25)	0

Figure 1: Duration of complete remission (CRD) and overall survival in all cohorts

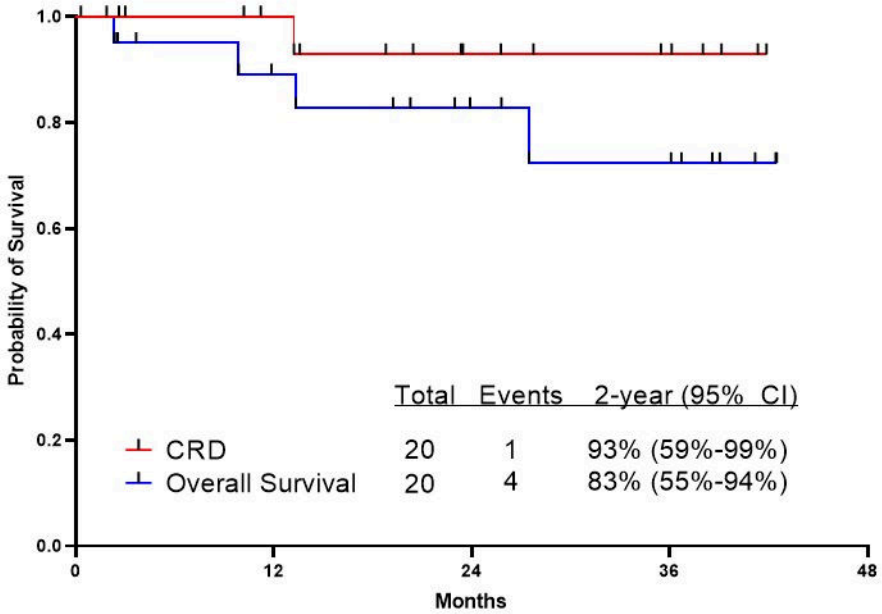

Figure 1

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