ELSEVIER

Blood 142 (2023) 2878–2881

The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

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

Phase 2 Trial of Mini-Hyper-CVD Plus Inotuzumab Ozogamicin, with or without Blinatumomab, in Older Patients with Newly Diagnosed Philadelphia Chromosome-Negative B-Cell Acute Lymphoblastic Leukemia

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Background

The introduction of inotuzumab ozogamicin (InO) and blinatumomab (blina) has drastically improved the overall survival (OS) of patients with relapsed/refractory B-cell acute lymphoblastic leukemia (B-ALL). Older patients with B-ALL have worse outcomes compared with younger patients due to the poor-risk biology of their disease and their inability to tolerate intensive chemotherapy. We aim to study the incorporation of InO and blina with low intensity chemotherapy in older patients with newly diagnosed (ND) B-ALL.

Methods

Adults ≥60 years with ND Philadelphia chromosome (Ph)-negative B-ALL who were untreated or had received up to two cycles of previous therapy were eligible. Other inclusion criteria included an Eastern Cooperative Oncology Group (ECOG) performance status of ≤3 and adequate organ function. Patients with central nervous system (CNS) disease were eligible.

Patients received mini-Hyper-CVD (mHCVD, cyclophosphamide 150mg/m ^{2} q12h D1-3, dexamethasone 20mg daily D1-4, 11-14, and vincristine 2mg D1, 8 alternating with methotrexate (MTX) 250mg/m ^{2} D1 & cytarabine 500mg/m ^{2} q12h D2, 3) for up to 8 cycles. Eight doses of intrathecal (IT) MTX /cytarabine were given for CNS prophylaxis; patients with CNS disease had IT hydrocortisone, MTX, and cytarabine twice weekly till CNS clearance, then weekly x4. Eight doses of rituximab 375mg/m ^{2} were given on D1, 8 of C1-4 if CD20 was ≥20% by flow cytometry. Initially, InO was given at 1.3-1.8mg/m ^{2} on D3 of C1 and 1.0-1.3mg/m ^{2} on D3 in C2-4. The protocol was amended from patient 50 such that InO was given in fractionated doses with a maximum cumulative dose of 2.7mg/m ^{2} (0.6 mg/m ^{2} on D2 of C1, 0.3 mg/m ^{2} on D8 of C1, then 0.3 mg/m ^{2} on D2 and D8 of C2-4). Ursodeoxycholic acid was given to all patients. Four cycles of blina 28μg/day replaced C5-8 of mHCVD + InO.

Maintenance was initially with vincristine 2mg D1, prednisolone 50mg daily D1-5, 6-mercaptopurine 50mg BID & MTX 10mg/m ^{2} weekly (POMP) for three years. After the protocol amendment, this was reduced to 12 cycles of POMP, with one cycle of blina given after every three POMP cycles (total four blina cycles).

Results

83 patients with a median age of 68y (range, 60 - 87; ≥70y, 34%) were enrolled (Table 1). Several patients had high-risk features: 25 (39%) harbored *TP53* mutations, 9 (18%) had a Ph-like signature, and 19 (23%) had high-risk cytogenetics (12 low hypodiploidy/near triploidy, 3 tetraploidy, 3 complex and 1 t(4;11)).

77 patients were not in CR at enrollment and evaluable for response. 76 (99%) responded, with 69 (90%) attaining CR. Among responders, 60 (79%) and 71 (94%) patients had no detectable minimal residual disease (MRD) by flow cytometry after C1 and overall, respectively. No early deaths were observed.

After a median follow-up of 88 months (IQR, 41-120), the median overall survival (OS) was 56 months (95%CI, 28-85), and the median progression-free survival (PFS) was 47 months (95% CI, 21-72). The 5-year continuous remission duration (CRD) and OS rates were 78% and 49%, respectively. The 5-year OS for patients aged 60-69 without adverse cytogenetics (n=40), age 60-69 with adverse cytogenetics (n=15), age ≥70 without adverse cytogenetics (n=24) and age ≥70 with adverse cytogenetics (n=4) were 73%, 27%, 39% and 0%, respectively.

Five (6%) patients underwent allogeneic stem cell transplantation (ASCT) in first CR, 12 (15%) relapsed, 33 (40%) remain in ongoing continuous remission without ASCT, and 33 (40%) died in remission. Of the 12 relapsing patients, 5 had extramedullary disease, all with CNS involvement. 12 (14%) patients died due to progressive disease at a median of 23 (range 2 - 78) months; these patients had a median age of 64 (range 60 - 79) years. Of the 33 who died in remission, nine were due to secondary myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML). The median age of these patients was 71 years (range, 64 - 87), with a median time to MDS/AML of 34 months (range, 7 - 75). Fourteen deaths in CR were due to treatment-related complications (9 sepsis, 3 veno-occlusive disease (VOD), 2 ASCT). Six (7%) patients developed veno-occlusive disease, 4/49 (8%) in the pre-amendment group and 2/34 (6%) in the post-amendment group.

Conclusion

Older patients with ND Ph-negative ALL treated with mHCVD plus InO, with or without blina had excellent response rates and deep remissions. However, further adjustment of the regimen is needed, especially in patients ≥70 years.

Disclosures Jabbour: *Genentech:* Consultancy, Honoraria, Research Funding; *Abbvie:* Consultancy, Honoraria, Research Funding; *Pfizer:* Consultancy, Honoraria, Research Funding; *Takeda:* Consultancy, Honoraria, Research Funding; *Bristol-Myers Squibb:* Consultancy, Honoraria, Research Funding; *Ascentage Pharma Group:* Consultancy, Honoraria, Research Funding; *Adaptive Biotech:* Consultancy, Honoraria, Research Funding; *Amgen:* Consultancy, Honoraria, Research Funding; *Hikma Pharmaceuticals:* Consultancy, Honoraria, Research Funding. **Short:** *Novartis:* Consultancy; *Amgen:* Honoraria; *Takeda:* Consultancy, Research Funding; *AstraZeneca:* Consultancy; *Stemline therapeutics:* Research Funding; *Astellas:* Research Funding; *Pfizer:* Consultancy. **Jain:** *ADC Therapeutics:* Research Funding; *Fate Therapeutics:* Research Funding; *Incyte:* Research Funding; *MEI Pharma:* Consultancy, Honoraria, Other: TRAVEL, ACCOMMODATIONS, EXPENSES; *BMS:* Consultancy, Honoraria, Other: Travel, Accommodations, Expenses, Research Funding; *TransThera Sciences:* Research Funding; *Ipsen:* Consultancy, Honoraria, Other: TRAVEL, ACCOMMODATIONS, EXPENSES; *Mingsight:* Research Funding; *Dialectic Therapeutics:* Research Funding; *TG Therapeutics:* Consultancy, Honoraria, Other: Travel, Accommodations, Expenses; *Pharmacyclics:* Consultancy, Honoraria, Other: Travel, Accommodations, Expenses, Research Funding; *Pfizer:* Research Funding; *Novalgen:* Research Funding; *Loxo Oncology:* Research Funding; *Medisix:* Research Funding; *Adaptive Biotechnologies:* Consultancy, Honoraria, Other: Travel, Accommodations, Expenses, Research Funding; *CareDX:* Consultancy, Honoraria, Other: Travel, Accommodations, Expenses; *Cellectis:* Consultancy, Honoraria, Other: Travel, Accommodations, Expenses, Research Funding; *Newave:* Research Funding; *Beigene:* Consultancy, Honoraria, Other: Travel, Accommodations, Expenses; *Takeda:* Research Funding; *AstraZeneca:* Consultancy, Honoraria, Other: Travel, Accommodations, Expenses, Research Funding; *Precision Biosciences:* Consultancy, Honoraria, Other: Travel, Accommodations, Expenses, Research Funding; *Servier:* Research Funding; *Kite/Gilead:* Consultancy, Honoraria, Other: Travel, Accommodations, Expenses, Research Funding; *Janssen:* Consultancy, Honoraria, Other: Travel, Accommodations, Expenses; *AbbVie:* Consultancy, Honoraria, Other: Travel, Accommodations, Expenses, Research Funding; *Genentech:* Consultancy, Honoraria, Other: Travel, Accommodations, Expenses, Research Funding; *Aprea Therapeutics:* Research Funding. **Kadia:** *SELLAS Life Sciences Group:* Research Funding; *Iterion:* Research Funding; *Genentech:* Consultancy, Research Funding; *Hikma Pharmaceuticals:* Speakers Bureau; *GenFleet Therapeutics:* Research Funding; *Glycomimetics:* Research Funding; *Cure:* Speakers Bureau; *Regeneron Pharmaceuticals:* Research Funding; *Sanofi-Aventis:* Consultancy; *Biologix, Cure, Hikma Pharmaceuticals:* Speakers Bureau; *Liberum:* Consultancy; *Celgene:* Research Funding; *Astellas Pharma Global Development:* Research Funding; *Jazz Pharmaceuticals, Pfizer, Pulmotect, Inc, Regeneron Pharmaceuticals, SELLAS Life Sciences Group:* Research Funding; *Amgen, Inc.:* Research Funding; *Ascentage Pharma Group:* Research Funding; *Cyclacel:* Research Funding; *Janssen Research and Development:* Research Funding; *Pfizer:* Consultancy, Research Funding; *Pulmotect, Inc.:* Consultancy, Research Funding; *Genzyme:* Honoraria; *Delta-Fly Pharma, Inc.:* Research Funding; *Novartis:* Consultancy; *Cellenkos Inc.:* Research Funding; *AstraZeneca:* Research Funding; *AbbVie, Amgen, Inc, Ascentage Pharma Group, Astellas Pharma Global Development, Astex, AstraZeneca, BMS, Celgene, Cellenkos Inc, Cyclacel, Delta-Fly Pharma, Inc, Genentech, Inc., Genfleet, Glycomimetics, Iterion, Janssen Research and Development:* Research Funding; *Daiichi Sankyo, Genentech, Inc., Genzyme, Jazz Pharmaceuticals, Liberum, Novartis, Pfizer, PinotBio, Inc, Pulmotect, Inc, Sanofi-Aventis, Servier:* Consultancy; *Agios:* Consultancy; *Servier:* Consultancy; *Pinotb-Bio:* Consultancy; *BMS:* Consultancy, Research Funding; *Astex:* Honoraria. **Daver:** *Kite, a Gilead company:* Consultancy, Research Funding; *Agios:* Consultancy; *Shattuck Labs:* Consultancy; *Syndax:* Consultancy; *Jazz:* Consultancy; *Novartis:* Consultancy; *AROG:* Consultancy; *Hanmi:* Research Funding; *Trillium:* Consultancy, Research Funding; *Trovagene:* Research Funding; *FATE:* Research Funding; *Novimmune:* Research Funding; *Glycomimetics:* Research Funding; *Celgene:* Consultancy; *Servier:* Consultancy, Research Funding; *Gilead:* Consultancy, Research Funding; *Pfizer:* Consultancy, Research Funding; *AbbVie:* Consultancy, Research Funding; *Amgen:* Consultancy, Research Funding; *ImmunoGen:* Consultancy, Research Funding; *Astellas:* Consultancy, Research Funding; *Genentech:* Consultancy, Research Funding; *Daiichi Sankyo:* Consultancy, Research Funding; *Bristol-Myers Squibb:* Consultancy, Research Funding; *Kronos Bio:* Research Funding. **Borthakur:** *Pacylex, Novartis, Cytomx, Bio Ascend::* Membership on an entity's Board of Directors or advisory committees; *Astex Pharmaceuticals, Ryvu, PTC Therapeutics:* Research Funding; *Catamaran Bio, Abbvie, PPD Development, Protagonist Therapeutics, Janssen:* Consultancy. **DiNardo:** *AbbVie/Genentech:* Honoraria; *Novartis:* Honoraria; *ImmuniOnc:* Honoraria; *Schrödinger:* Consultancy; *Notable Labs:* Honoraria; *Fogham:* Honoraria; *BMS:* Honoraria; *Takeda:* Honoraria; *Astellas:* Honoraria; *Servier:* Honoraria. **Ravandi:** *Astellas:* Consultancy, Honoraria, Research Funding; *Xencor:* Research Funding; *Abbvie:* Consultancy, Honoraria, Research Funding; *Syros:* Consultancy, Honoraria, Research Funding; *Amgen:* Honoraria, Research Funding; *Biomea fusion:* Honoraria, Research Funding; *Prelude:* Research Funding; *Astex/taiho:* Membership on an entity's Board of Directors or advisory committees, Research Funding;

Celgene/BMS: Consultancy, Honoraria, Research Funding. **Kantarjian:** *AstraZeneca/MedImmune:* Honoraria; *Amgen:* Honoraria; *Ascentage Pharma Group:* Honoraria; *Astellas Pharma:* Honoraria; *Abbvie:* Consultancy, Honoraria; *Daiichih-Sankyo (Inst):* Honoraria, Research Funding; *Immunogen (Inst):* Honoraria, Research Funding; *Ipsen:* Honoraria; *Jazz Pharmaceuticals (Inst):* Honoraria, Research Funding; *KAHR Medical:* Honoraria; *Novartis:* Honoraria; *Pfizer:* Honoraria; *Precision Biosciences:* Honoraria; *Shenzhen Target Rx:* Honoraria; *Taiho Pharmaceutical:* Honoraria; *Abbvie (Inst):* Research Funding; *Amgen (Inst):* Research Funding; *Ascentage Pharma (Inst):* Research Funding; *Bristol-Myers Squibb (Inst):* Research Funding; *Novartis (Inst):* Research Funding.

Table 1. Baseline patient characteristics

Characteristic	Category	N (%) / Median [range]
Age (years)		68 [60 - 87]
	≥70	28 (34)
Cytogenetics	Diploid	27 (33)
	HeH	5 (6)
	Ho-Tr	12 (14)
	Tetraploidy	3 (4)
	Complex	3 (4)
	t(4;11)	1 (1)
	Misc	16 (19)
	IM/ND	16 (19)
CD19 (%)		99.6 [26-100]
CD22 (%)		96.9 [27-100]
CD20	≥20%	46/76 (61)
Ph-like ALL		9/50 (18)
***TP53* mutation**		25/64 (39)

HeH, high hyerdiploidy, Ho-Tr, low hypodiploidy / near triploidy, IM/ND, insufficient metaphases / not done.

Figure 1. Continuous remission duration (CRD) and overall survival (OS) in the study cohort

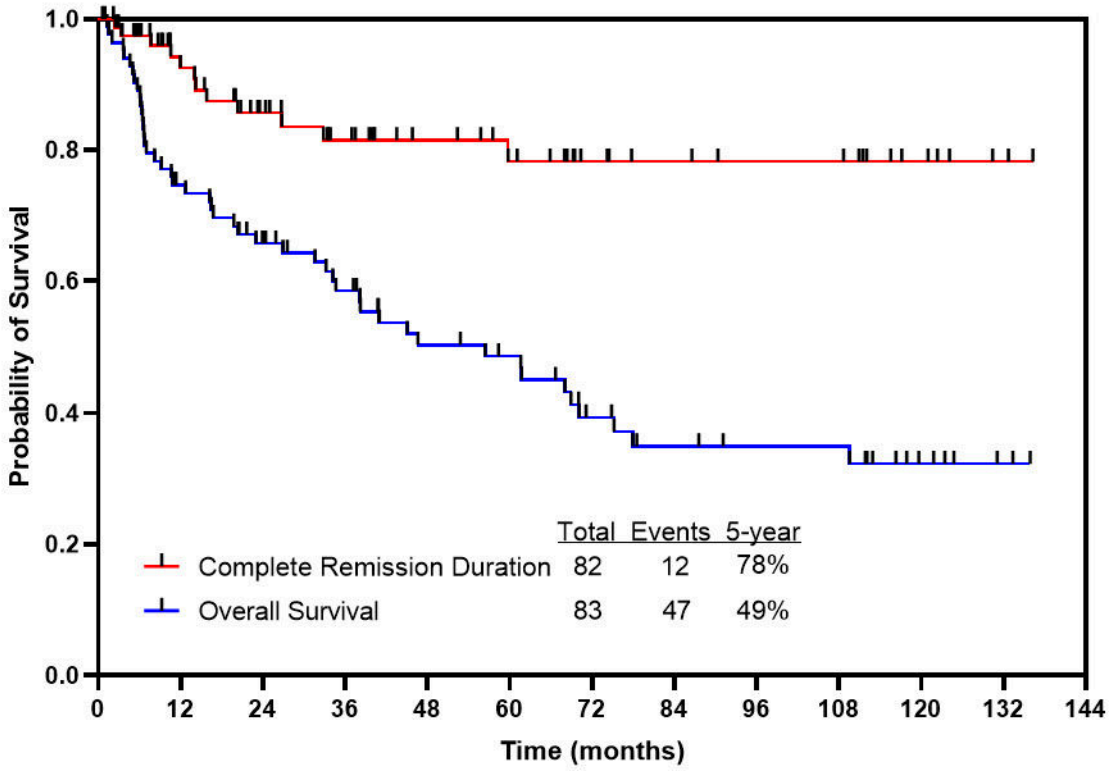

Figure 1

https://doi.org/10.1182/blood-2023-182982