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Blinatumomab Consolidation for Adult B-Cell Acute Lymphoblastic Leukemia in First and Second Complete Remission

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Abstract:

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Although the outcome of adult patients with B-cell precursor acute lymphoblastic leukemia (BCP-ALL) has dramatically improved in the last decades, patients with adverse genetic subtypes and/or persistence of minimal residual disease (MRD) are still at high risk of relapse. When treated with standard chemotherapy, adult patients with Philadelphia (Ph)-

negative BCP-ALL in first relapse have a dismal prognosis, with a median overall survival (OS) of approximately 6 months and a 5-year OS rate of less than 20%.[1,2]

Blinatumomab is a CD3/CD19 bispecific T-cell engager, which induces T-cell cytotoxicity against CD19-positive B-cells. The drug was first approved in relapsed/refractory (R/R) Ph-negative BCP-ALL based on the results of the phase 3 TOWER study showing a higher overall response rate (44% *versus* 25%, p<0.001) and a longer median overall survival (7.7 *versus* 4.0 months, p=0.01) when compared to standard of care.[3] Blinatumomab was further approved for BCP-ALL patients with persistent or reappearing MRD based on the results of the phase 2 BLAST study.[4]

More recently, two phase 3 studies in children, adolescents, and young adults with BCP-ALL in first relapse suggested that blinatumomab used as consolidation after salvage therapy was more efficient and better tolerated than chemotherapy. Patients who received blinatumomab also showed better MRD response and greater likelihood of proceeding to alloHSCT compared to chemotherapy alone. [5,6] Moreover, the use of blinatumomab after an attempt to reduce the leukemic burden rather than in overt relapse is now supported by many real-world studies or retrospective analyses of prospective trials showing the prognostic impact of bone marrow tumor infiltration prior to blinatumomab administration.[7–10] In the present real-world study, we aim at describing the outcome of adult patients who received blinatumomab in first or second complete remission. As internal comparator, we also reported on patients from the same institutions who received blinatumomab in overt relapse.

The study was conducted at Saint-Louis university hospital in Paris and at Città della Salute e della Scienza university hospital in Turin. One hundred and fifteen BCP-ALL patients consecutively treated between April 2012 and June 2021 were retrospectively included. We

included patients who received commercial blinatumomab 1) in first complete remission (CR1), 2) in second complete remission (CR2), or 3) in overt relapse or refractory (R/R). Among the 115 patients included, 68 (59%) patients were treated in CR1, 31 (27%) patients in CR2 after chemotherapy-base salvage therapy usually combined to tyrosine kinase inhibitor (TKI) in Philadelphia-positive (Ph+) ALL (**Supp. Table 1**), and 16 (14%) patients in overt relapse or refractory. The median age was 37 years (range 16-84) and 28/115 (24%) were Philadelphia (Ph)-positive. Patients in CR1 mostly received blinatumomab for MRD persistence (n=59/68, 87%) or due to inability to receive standard consolidation (n=9/68, 13%, off-label use) because of chemotherapy toxicity (including one specifically related to asparaginase) in 8 cases and to low performance status in one case (**Table 1**). Patients in CR2 received blinatumomab for R/R disease and underwent a debulking strategy before blinatumomab. The number of blinatumomab cycles along with the use of chemotherapy and/or of allogeneic hematopoietic stem cell transplant (alloHSCT) after blinatumomab was up to physician choice. The majority of Ph+ ALL patients (26/28) received a combination of blinatumomab and TKI (14 ponatinib, 4 nilotinib, 4 imatinib, 4 dasatinib). In the vast majority of patients, MRD was assessed by immunoglobulin/T-cell receptor (IG/TR) clonospecific qPCR (99/115, 86%). The other patients were monitored by BCR::ABL1 qPCR (8/115, 7%), flow cytometry (6/115, 5%), *KMT2A*-r transcript qPCR (2/115, 2%). The study was authorized by the ethical committees of both institutions and conducted in accordance with the Declaration of Helsinki.

In the 3 subgroups, the median number of blinatumomab cycles given was 2 (range, 1-6). A cytokine release syndrome grade ≥ 3 was reported in 2 patients. An immune effector cell-associated neurotoxicity syndromes ≥ 3 was observed in 11 patients (Table S2). Nineteen patients (16.5%) had to temporary interrupt blinatumomab because of adverse events, while

in 4 (3.5%) patients, blinatumomab was permanently discontinued (ICANS in 2 cases, ICANS and CRS in 1 case and serious infection in 1 case). In R/R patients, a complete remission was reached after blinatumomab in 9/16 (56%), among whom 4 were bridged to allo-HSCT in continuous complete remission (CCR). The median DFS and OS were 6.0 and 10.8 months, in line with the results of TOWER study.[3] In the CR subgroups, a complete MRD-response was achieved after one blinatumomab cycle in 83% of CR1 and 86% of CR2 patients (p=.99). Forty-six patients (42%) treated in CR (41% CR1, 45% CR2) were bridged to allo-HSCT in CCR after blinatumomab with 68% of all transplanted patients being in complete MRD response at the time of transplant. Twenty patients treated in CR relapsed, 12 from the CR1 cohort and 8 from the CR2 cohort. Eight patients had a CNS relapse (40%), among whom 7 patients had a combined relapse. After a median follow up of 3.1 years (95%CI[2.4-3.7]), the 3-year cumulative incidence of relapse was 23% for CR1 and 26% for CR2 patients (p=0.31), the 3-year DFS was 68% for CR1 and 67% for CR2 patients (p=0.41), and the 3-year OS was 80% for CR1 and 71% for CR2 patients (p=0.32) (**Figure 1A/B**). Among Ph-negative ALL patients younger than 70 years old who received blinatumomab in CR1 before any transplant, 25/47 (53%) were bridged to allo-HSCT in CCR. Among these 47 patients, 17 were alive in CCR after 3 years of follow-up, 7 without and 10 after allo-HSCT. A time-dependent analysis of allo-HSCT in these patients did not suggest a benefit of transplant neither for DFS (SHR 2.9, 95%CI[0.80-10.4], p=0.11 by the Mantel-Byar test), nor for OS (SHR 5.5, 95%CI[0.82-37.6], p=0.08 by the Mantel-Byar test) (Figure S3). Considering the 99 patients treated in CR, univariate analysis showed that MRD levels before blinatumomab and best MRD response after blinatumomab were significantly associated with DFS and OS (**Figure 1C/D, Suppl. Figures S1/S2**). Patient characteristics, disease-related features, and allo-HSCT performed in continuous complete remission (time-dependent analysis) did not predict DFS or OS in

univariate analysis (**Table S2**). Both pre- and post-blinatumomab MRD levels retained significance in bivariate analysis for DFS and OS (**Figure 1E**).

Our observation underlines the efficacy of blinatumomab in consolidation after chemotherapy-base salvage, showing comparable outcomes between patients treated in CR2 and CR1. Similar proximity between CR1 and CR2+ patients' outcome was already noted in the phase 2 BLAST study for patients with positive MRD.[11] In this study the median survival of CR1 and CR2+ patients with a MRD ≥ 10^{-3} before blinatumomab was 41.2 versus 23.1 months, respectively (p=0.4). In CR2 patients, promising DFS and OS were observed as compared to historical cohorts of patients treated with chemotherapy alone or with blinatumomab in overt relapse.[1–3] Our results corroborate those reported in two phase 3 trials by Brown et al. and Locatelli et al., performed in children, adolescents, and young adults in second complete remission of intermediate and high-risk Ph-negative BCP-ALL. In the study by Brown et al., the 2-year DFS was 54% for the blinatumomab group vs. 39% for the chemotherapy group (HR 0.70, 95% CI 0.47-1.03) and the 2-year OS was 71% vs 58%, respectively (HR 0.62, 95% CI 0.39-0.98).[6] In the study by Locatelli et al., 2-year estimated EFS was 66% in the blinatumomab group and 27% in the chemotherapy group (HR 0.33, 95% CI 0.18-0.61) and OS was 85% and 70%, respectively (HR 0.43, 95% CI 0.18-1.01).[5] Whereas these two randomized trials have led to important changes in pediatric clinical practice,[12] the present study suggests that similar strategies using blinatumomab in consolidation and not in overt relapse should be considered in adults. Indeed, a second complete remission may be achieved in up to 60-70% after standard chemotherapy for late relapse,[1,13] or after inotuzumab ozogamicin.[14]

Moreover, our study suggests a strong benefit of consolidation with blinatumomab in patients who achieved a complete MRD response before exposure to blinatumomab. In our

cohort, these patients were mostly CR1 patients who presented toxicity to prior chemotherapy, or CR2 patients with favorable response to salvage therapy. Such a benefit of consolidation with blinatumomab in CR1 MRD-negative patients was recently evidenced by the E1910 ECOG phase 3 study that showed a dramatic improvement of OS for patients exposed to blinatumomab (HR 0.42, 95% CI: 0.24-0.75).[15] It should be emphasized that the significant incidence of CNS relapses highlighted in our report underscores the critical necessity for adequate CNS prophylaxis among patients treated with blinatumomab.

Finally, our study underscores the significance of both pre- and post-blinatumomab MRD as predictors of patient outcomes. While the role of allo-HSCT is being strongly questioned due to the increased utilization of blinatumomab as a frontline treatment, it is important to consider high levels of pre-blinatumomab MRD and/or detectable post-blinatumomab MRD as cautionary indicators that can guide therapeutic decisions after blinatumomab treatment. These MRD assessments provide valuable insights to inform post-blinatumomab treatment strategies and optimize patient outcomes.

Author contributions

I.U., E.L., and N.B. designed the research, analyzed the data and wrote the manuscript. I.U., E.L., F.R., M.C., F.C., D.F., M.S., N.D., R.I., L.A., E.R., H.D., E.A., and N.B. managed the patients and provided clinical data. R.K., D.F., and E.C. performed disease characterization and MRD analyses. All authors reviewed and approved the manuscript.

Conflict of interest disclosure

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Figure 1: Patients' outcome by disease status and MRD before and after blinatumomab.

DFS (A) and OS (B) for patients in 1st CR (CR1), 2nd CR (CR2), or overt relapse (R/R). DFS (C) and OS (D) for CR1/2 patients according to pre-blinatumomab MRD and to best MRD response after blinatumomab. Bivariate cox model (E) for DFS and OS with MRD prior to blinatumomab and after blinatumomab as covariates. MRD+ indicates any detectable MRD.

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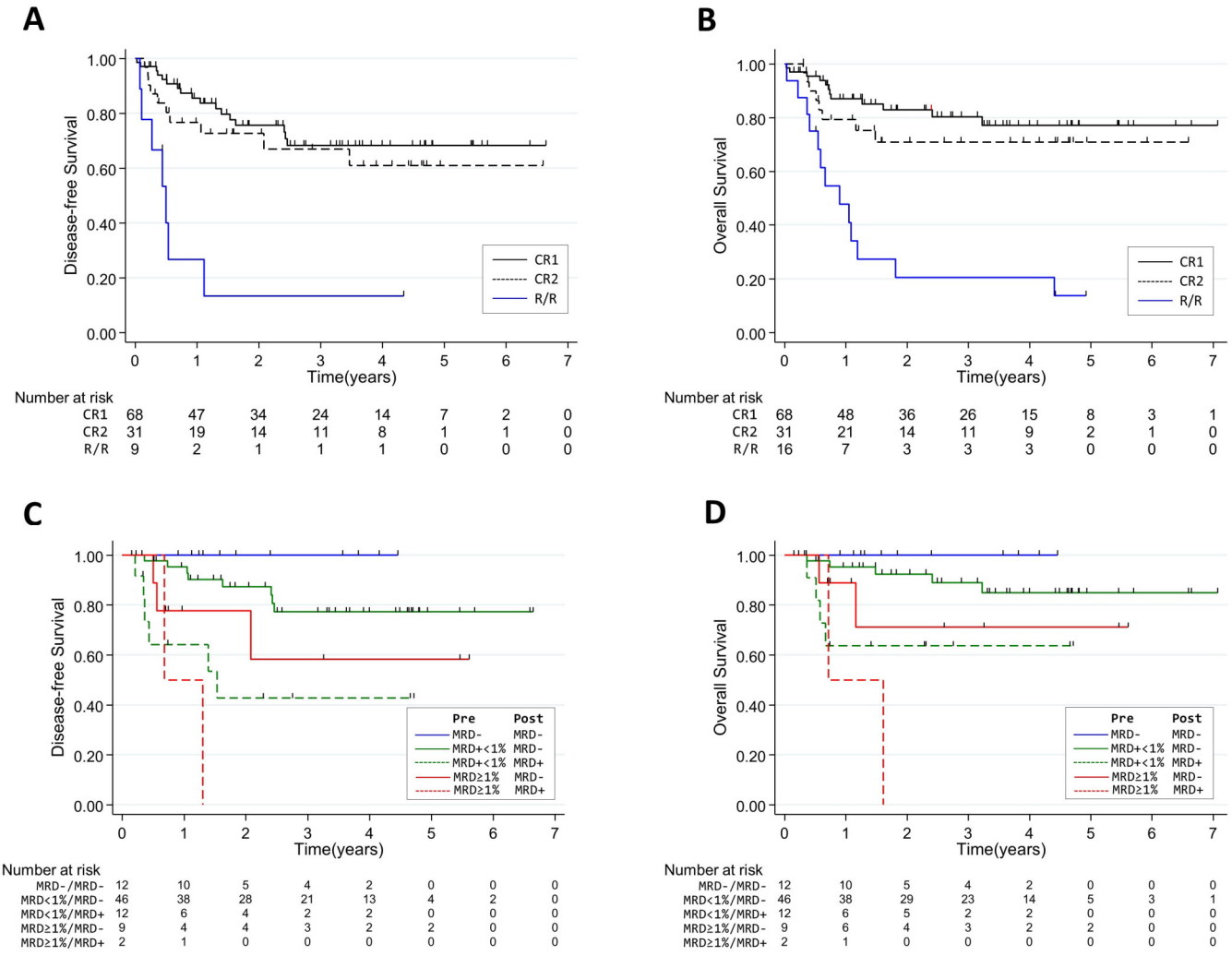
Table 1. Baseline patients and disease characteristics compared according to study group

	1st CR [N=68]	p value	2nd CR [N=31]	p value	R/R [N=16]
Patient characteristics					
Age (years), median (range)	42 (17-84)	*0.91*	39 (16-77)	*0.95*	30 (20-76)
Sex (female), n (%)	31/68 (46)	*0.19*	19/31 (61)	*0.07*	5/16 (31)
Baseline disease characteristics					
WBC (x 10^9/L), median (range)	17.5 (1-730)	*0.09*	9 (1-325)	*0.23*	24 (1-600)
Pro-B phenotype, n (%)	14/68 (21)	*0.15*	4/31 (13)	*0.99*	2/16 (17)
***BCR::ABL1*, n (%)**	16/68 (24)	*0.15*	12/31 (39)	*0.004*	0/16 (0)
***KMT2A*-r, n(%)**	10/60 (17)	*0.09*	1/31 (7)	*0.03*	3/9 (21)
***IKZF1*del, n(%)**	22/55 (40)	*0.81*	10/28 (35)	*0.39*	1/8 (13)
CNS disease, n (%)	8/68 (12)	*0.27*	1/31 (3)	*0.10*	3/15 (20)
Non-CNS EM disease, n (%)	15/68 (22)	*0.99*	6/31 (19)	*0.71*	4/15 (27)
Blin indications, n (%)					
CR, MRD+	56/68 (82)	/	N/A	/	N/A
CR, MRD-	9/68 (13)	/	N/A	/	N/A
Refractory disease	N/A	/	N/A	/	2/16 (13)
Relapse	N/A	/	31/31 (100)	*0.11*	14/16 (87)
Pre-blin therapies, n (%)					
Allo-HCT	1/68 (1)	*0.23*	2/31 (6)	*0.04*	5/16 (31)
CAR T-cells	0/68 (0)	/	0/68 (0)	*0.34*	1/16 (6)
Inotuzumab ozogamicin	5/68 (7)	*0.27*	5/31 (16)	*0.65*	1/16 (6)
Blin therapy					
Number of cycles, median (range)	2 (1-6)	*0.24*	2 (1-6)	*0.35*	2 (1-4)

Abbreviations: CR, complete remission; R/R, relapse and refractory; WBC, white blood cells; CNS, central nervous system; EM, extramedullary; blin, blinatumomab; MRD, measurable residual disease; MRD+, any detectable MRD; Allo-HCT, allogeneic hematopoietic stem cell transplant; CAR, chimeric antigen receptor

Figure 1



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	DFS			OS		
MRD level	**HR**	**IC95%**	**P value**	**HR**	**IC95%**	**P value**
Pre blin*	3.03	1.21-7.59	0.018	3.01	1.04-8.73	0.042
Post blin, best response**	4.88	1.94-12.31	0.001	5.10	1.67-15.51	0.004

* 3 MRD levels : MRD-, MRD+<1%, MRD≥1%
** MRD+ *vs.* MRD-