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Combining blinatumomab and donor lymphocyte infusion in B-ALL patients relapsing after allogeneic hematopoietic cell transplantation: a study of the SFGM-TC

Paul Chauvet[1✉], Annalisa Paviglianiti[2,3], Myriam Labopin[2], Hélène Labussière[4], Nicolas Boissel[5,6], Marie Robin[6], Natacha Maillard[7], Marie Ouachée-Chardin[8], Edouard Forcade[9], Xavier Poiré[10], Sylvain Chantepie[11], Anne Huynh[12], Claude Eric Bulabois[13], Mathieu Leclerc[14], Sébastien Maury[14], Patrice Chevallier[15], Thomas Cluzeau[16], Jean-Baptiste Mear[17], Jérôme Cornillon[18], Karin Bilger[19], Célestine Simand[19], Yves Beguin[20], Marie-Thérèse Rubio[21], Ibrahim Yakoub-Agha[1,22] and Eolia Brissot[2✉]

Relapsed B-cell acute lymphoblastic leukemia (B-ALL) after allogeneic stem cell transplantation (allo-HCT) still represents a major concern with poor outcomes. The aim of this study is to compare the efficacy and safety of blinatumomab and donor lymphocyte infusion (DLI) versus blinatumomab alone in this setting. This is a multicenter retrospective study from centers of SFGM-TC. All transplanted patients who received blinatumomab salvage therapy were included. Patients who received DLI from 1 month before to 100 days after the starting of blinatumomab were included in the blina-DLI group. Seventy-two patients were included. Medium follow-up was 38 months. Fifty received blinatumomab alone and 22 the association blinatumomab-DLI. Two-year overall survival (OS) was 31% in the blinatumomab group and 43% in the blinatumomab-DLI group ($p = 0.31$). Studying DLI as a time dependent variable, PFS did not significantly differ between the 2 groups (HR:0.7, 95% CI: 0.4–1.5). In multivariate analysis, DLI was not a prognostic factor for OS, progression-free survival and progression/relapse incidence. Adverse events and graft-versus-disease rates were comparable in the 2 groups. In conclusion, adding DLI between 1 month before and 100 days after start of blinatumomab is safe and does not seem to improve outcomes in B-ALL patients who relapsed after allo-HCT.

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INTRODUCTION

Allogeneic hematopoietic cell transplantation (allo-HCT) is still a standard of treatment in a subset of patients with B-cell acute lymphoblastic leukemia (ALL) [1]. However, post-transplant relapse is associated with poor outcome with a median overall survival (OS) below 6 months [2–4]. In addition, approximately 60–70% of the patients never achieve a second remission [5]. Despite recent improvements in ALL treatment, therapeutic options for post-transplant relapse remain limited. Especially, chemotherapy alone does not seem to be an effective option as reported in previous studies [2, 6].

Over the last decades, donor lymphocyte infusion (DLI) has been used as a salvage therapy after post-transplant relapses in B-ALL patients with a proven antileukemic effect [7, 8]. Nevertheless, the complete response rate does not exceed 30% in prospective studies or systematic reviews, and long-lasting control of the disease is rare [9–11]. In addition, DLI can trigger graft-versus-host disease (GVHD) [12] that can be responsible for high incidence of morbidity and mortality. Second allo-HCT is not always feasible, and outcome after second transplant seems to be similar to those observed after DLI [13, 14].

Blinatumomab (blina), a CD3/CD19 bispecific antibody acting as a T-cell engager, has been approved in the treatment of refractory/relapsed B-ALL [15]. A few publications reported the association of blina and DLI in the literature. Stein et al. reported the use of blina in B-ALL patients who relapsed after allo-HCT

[1]CHU de Lille, Maladies du Sang, Université de Lille, 59000 Lille, France. [2]Sorbonne University, INSERM UMR-S 938, Saint-Antoine Research Centre, AP-PH, Department of Clinical Hematology and Cellular Therapy, Saint-Antoine Hospital, Paris, France. [3]Institut Català d'Oncologia, Cell Transplant/Cell Therapy Unit, Barcelona, Spain. [4]Hospices Civils de Lyon, Lyon-Sud Hospital, Clinical Hematology, Pierre-Bénite, France. [5]Université de Paris Cité, Institut de Recherche Saint-Louis, URP-3518, Assistance Publique-Hôpitaux de Paris, University Hospital Saint-Louis, 75010 Paris, France. [6]Hôpital Saint Louis, Assistance Publique Hôpitaux de Paris, Université de Paris, Paris, France. [7]Service d'Hématologie, CHU de Poitiers, Poitiers, France. [8]Institute of Pediatric Hematology and Oncology (IHOPe), Lyon, France. [9]Service d'Hématologie Clinique et Thérapie Cellulaire, CHU Bordeaux, F-33000 Bordeaux, France. [10]Section of Hematology, Cliniques Universitaires St-Luc, Université Catholique de Louvain, Brussels, Belgium. [11]Institut d'Hématologie de Basse Normandie, CHU Caen, Caen, France. [12]CHU – IUCT O, 31059 Toulouse, Toulouse, France. [13]CHU Grenoble Alpes, Grenoble, France. [14]Service d'Hématologie et de Thérapie Cellulaire, Hôpital Henri Mondor, Créteil, France. [15]University of Nantes, CHU Hôtel Dieu, Nantes, France. [16]Université Nice Côte d'azur, CHU de Nice, Nice, France. [17]CHU de Rennes, 2, rue Henri-Le-Guilloux, 35000 Rennes, France. [18]Département d'Hématologie Clinique et de Thérapie Cellulaire, CHU de Saint Etienne, Saint-Priest-en-Jarez, France. [19]Service d'Hématologie, Institut de cancérologie Strasbourg Europe (ICANS), Strasbourg, France. [20]Division of Haematology, Department of Medicine, University and CHU of Liège, Liège, Belgium. [21]Service d'Hématologie, Hôpital Brabois, CHRU Nancy, Equipe 6 IMoPa, Biopole de L'université de Lorraine, CNRS UMR 7563 Nancy, France. [22]CHU de Lille, université de Lille, Inserm U1286, Infinite, 59000 Lille, France. ✉email: chauvet.paul@outlook.fr; eolia.brissot@aphp.fr

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describing a CR rate of 45% with a median relapse free survival of 7 months in responders [16].

We conducted a retrospective multicenter study on B-ALL patients who relapsed following allo-HCT in order to compare the safety and efficacy of blina versus blina in association with DLI.

METHODS

Patients and data collection

Seventy-two allografted adult or pediatric B-ALL patients who received blina with or without DLI as a salvage therapy after post-transplant relapse were included. Only patients who received at least one complete cycle of blina were included. Patient received blina alone or blina and DLI according to center policy. Blina and DLI exact modalities were at the discretion of each center. Of note, a cycle of blina consisted of 28 days of continuous intravenous infusion of blina followed by a period of 14 days of treatment-free interval [17].

The study was conducted between January 2012 and December 2018 in 25 centers belonging to the Francophone Society of Bone Marrow Transplantation and Cellular Therapy (SFGM-TC). This study was approved by the SFGM-TC scientific board and was conducted in agreement with the declaration of Helsinki. Clinical data were obtained from the ProMISe (Project Manager Internet Server) database. All patients or their legal representative provided written informed consent for the use of their data for clinical research.

Statistical analysis

Complete response (CR) was defined as the presence of less than 5% blasts in the bone marrow with no extramedullary disease (e.g., central nervous system or soft tissue disease) associated with peripheral hematologic recovery.

Minimal residual disease (MRD) response was defined as a CR without any detectable disease, irrespective of the employed marker (e.g., rearranged immunoglobulin gene) or technic (Sanger, polymerase chain reaction, next generation sequencing or multiparametric flow cytometry).

Adverse events (AE) were recorded and classified according to the Common Terminology Criteria for Adverse Events (CTCAE) [18].

GVHD was recorded using the modified Glucksberg criteria for acute GVHD (aGVHD) [19] and the 2014 revised National Institutes of Health (NIH) Consensus Conference criteria for chronic GVHD (cGVHD) [20].

Patients who received a DLI from 1 month before to 100 days after start of blina were included in the blina-DLI group. Patient's disease, and transplant-related characteristics for the two cohorts (blina alone / blina-DLI) were compared by using χ^2 or Fisher statistics for categorical variables and the Mann-Whitney test for continuous variables.

The primary endpoint was OS defined as the time from the start of blina treatment to death or last follow-up. Patients alive at last follow-up were censored.

The secondary endpoints were CR after blina, progression-free survival (PFS), relapse/progression, non-relapse mortality (NRM), AE and GVHD occurring after blina. PFS was defined as survival with no evidence of relapse or progression. Relapse was defined as the presence of 5% BM blasts and/or reappearance of the underlying disease. Patients who did not experience CR were considered as relapsed at time of no CR. Patients alive without disease at last follow-up were censored. NRM referred to death from any cause without previous leukemia relapse/progression.

Cumulative incidence was used to estimate the endpoints of CR and relapse/progression, death being the competing event. Probabilities of OS and PFS were calculated using the Kaplan–Meier method. Comparison between the 2 groups was performed using extended Cox model including DLI as a time dependent variable. In addition, a landmark analysis was performed for comparison of OS in patients alive at day 100 post blina. Multivariate analysis was adjusted on patient age, patient sex, donor type (matched sibling donor (MSD) vs other), time from allo-HCT to relapse and time from relapse to blina.

Analyses were performed with SPSS 25 SPSS 27 (IBM SPSS Statistics for Windows, IBM Corp, Armonk, NY) and R 4.1.1 (R Core Team (2021). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/) software packages.

RESULTS

Patients and treatment characteristics

Seventy-two patients were identified. The baseline characteristics of patients are reported in Table 1. Fifty (69%) patients received blina as a single treatment (blina group) for relapse while 22 (31%) received blina in association with DLI (blina-DLI group). There were no significant differences between the two groups in terms of patient and disease characteristics. Male gender accounted for 54% of the patients in the blina group and 68% in the blina-DLI group. The age distribution did not significantly differ between the two groups and the pediatric population accounted for 3 (6%) and 4 (18%) of blina and blina-DLI groups, respectively, $p = 0.11$. Thirteen patients had Philadelphia chromosome B-ALL subtype (PH + ALL) in the blina group and 7 in the blina-DLI group. Thirteen patients (18%) had received blina prior to allo-HCT, 7 (14%) in the blina group and 6 (27%) in the blina-DLI group ($p = 0.85$). One patient received inotuzumab before allo-HCT-allo. Three patients received rituximab at the first line therapy and one patient received rituximab after first line therapy. Disease status at the time of allo-HCT, 45 (90%) of the blina group were in CR and 19 (86%) in the blina-DLI group.

Types of donors and cell source did not significantly differ between the two groups ($p = 0.31$ and $p = 0.2$, respectively). For the seven patients who received a haploidentical donor, the prophylaxis associated post-transplant cyclophosphamide; among which 5 were in the blina group and 2 in the blina-DLI group. Fifty-seven patients (79%) received myeloablative conditioning (MAC) regimen while 15 (21%) received reduced-intensity conditioning (RIC). MAC was used in 80% of patients in the blina group and 77% of patients in the blina-DLI group ($p = 0.76$). Total body irradiation (TBI) was part of the conditioning in 28 (56%) and 15 (68%) patients in blina and blina-DLI groups, respectively ($p = 0.33$). ATG was used in 36 (72%) patients in the blina group and in 8 (36%) in the blina-DLI group ($p = 0.004$).

As shown in Table 1, prior to B-ALL relapse, 22 patients (44%) of the blina-group and 6 (27%) of the blina-DLI group developed acute GVHD including 13 (26%) with grade ≥2 in the blina group and 4 (18%) with grade ≥2 int the blina-DLI group. Twelve patients from the blina group (24%) and 5 (23%) from the blina-DLI group developed chronic GVHD including 9 and 3 patients with extensive form respectively.

Post-transplant and pre-relapse anti-leukemia prophylaxis

Twelve patients (17%) received a variety of post-transplant anti-leukemia prophylaxis according to institutional guidelines (i.e., tyrosine kinase inhibitors, prophylactic cranial irradiation and intrathecal chemotherapy injection). Of note, none of the patients received blina before relapse.

Characteristics and management of post-HCT relapse

Disease relapse/progression was only molecular in 7 patients (11%) and overt (hematological) in 59 patients (89%) including 17 patients with extramedullary disease. These rates did not significantly differ between groups ($p = 0.93$). Main features of progression/relapse are described in Table 2.

Patients received a median number of 2 [IQR1–3] cycles of blina in the blina group and 3 [IQR2–4] cycles in the blina-DLI group ($p = 0.01$). Blina was initiated in a median time of 22 days [IQR 10–62] after relapse. This period was 19 days [IQR 10–50] in the blina group and 22 [IQR 13–92] in the blina-DLI group ($p = 0.27$). Blina was the first salvage therapy administered after allo-HCT in 40 patients (61%). This rate accounted for 67% of patients in the blina group and 48% in the blina-DLI group ($p = 0.14$). Blina administration modality followed the guidelines for blinatumomab which have been previously published [15, 21].

DLI was administered after a median time of 44 days [IQR 35–74] after blina initiation. Two patients received DLI before blina: 1

Table 1. Baseline characteristics of patients.

Characteristics	Blina alone ($n = 50$)	Blina–DLI ($n = 22$)	*P*	Overall ($n = 72$)
Patient				
Yr of HCT, median (range)	2015 (2011–2018)	2016 (2013–2018)	0.088	2015 (2011–2018)
Male sex, *n* (%)	27 (54%)	15 (68%)	0.26	42 (58%)
Age at HCT, median [IQR]	34.5 [26.2–57.5]	33.5 [19.5–49]	0.15	34.5 [21.8–54]
Age <18 y	3 (6%)	4 (18%)	0.11	7 (10%)
ALL Ph+ subtype	13 (26%)	7 (32%)	0.61	20 (28%)
Number of lines before HCT median (min-max)	2 (1–9)	2 (1–5)	0.75	2 (1–9)
Missing data	3	2		5
Blina before HCT, *n* (%)	7 (14%)	6 (27%)	0.2	13 (18%)
Disease status before HCT, *n* (%)			0.85	
CR MRD negative	19 (38%)	9 (41%)		28 (39%)
CR MRD positive	5 (10%)	3 (14%)		8 (11%)
CR MRD unknown	21 (42%)	7 (32%)		28 (39%)
Progressive disease	5 (10%)	3 (14%)		8 (11%)
Allo-HCT				
Type of donor, *n* (%)			0.31	
MSD	15 (30%)	12 (55%)		27 (38%)
MUD	19 (38%)	6 (27%)		25 (35%)
MMUD	8 (16%)	2 (9%)		10 (14%)
Haploidentical	4 (8%)	2 (9%)		6 (8%)
CB	4 (8%)	0 (0%)		4 (6%)
Cells source *n* (%)			0.2	
BM	10 (20%)	8 (36%)		18 (25%)
PB	36 (72%)	14 (64%)		50 (69%)
CB	4 (8%)	0 (0%)		4 (6%)
Donor age, median [IQR]	31 [23–44]	32.5 [20–45]	0.96	31 [23–44.5]
Missing data	1	0		1
Donor sex Male, *n* (%)	31 (62%)	14 (64%)	0.89	45 (63%)
MAC, *n* (%)	40 (80%)	17 (77%)	0.76	57 (79%)
Use of ATG, *n* (%)	36 (72%)	8 (36%)	0.004	44 (61%)
TBI, *n* (%)	28 (56%)	15 (68%)	0.33	43 (60%)
Post-HCT				
Best response after HCT, *n* (%)			0.19	
CR MRD negative	24 (48%)	9 (41%)		33 (46%)
CR MRD positive/NA	21 (42%)	7 (32%)		28 (39%)
Progression	5 (10%)	6 (27%)		11 (15%)
Prophylaxis of relapse, *n* (%)	5 (10.2%)	7 (33%)	0.034	12 (17%)
Missing data	1	1		2
aGVHD grade, *n* (%)			0.65	
No aGVHD	28 (56%)	16 (73%)		44 (61%)
I	9 (18%)	2 (9%)		11 (15%)
II	8 (16%)	3 (14%)		11 (15%)
III	3 (6%)	1 (5%)		4 (6%)
IV	2 (4%)	0 (0%)		2 (3%)
cGVHD, *n* (%)	12 (24%) (9 extensive)	5 (23%) (3 extensive)	0.91	17 (24%) (12 extensive)

ALL acute lymphoblastic leukemia, *allo-HCT* allogeneic hematopoietic stem cell transplantation, *aGVHD* acute graft versus host disease, *ATG* anti-thymocyte globulin; blina, blinatumomab, *BM* bone marrow, *CB* cord blood, *cGVHD* chronic graft versus host disease, *CR* complete response, *DLI* donor lymphocyte infusion, *MAC* myeloablative conditioning, *MSD* matched sibling donor, *MUD* matched unrelated donor, *MMUD* mismatched unrelated donor, *MRD* minimal residual disease, *NA* not available, *PB* peripheral blood, *TBI* total body irradiation, *Yr* year.

Table 2. Post-transplant relapse and treatment.

Characteristics	Blina alone ($n = 50$)	Blina - DLI ($n = 22$)	P	Overall ($n = 72$)
Type of relapse, *n* (%)			0.93	
Bone marrow	29 (64%)	13 (62%)		42 (64%)
Extra-medullary only	3 (7%)	1 (5%)		4 (6%)
Bone marrow and EM	9 (20%)	4 (19%)		13 (20%)
Molecular only	4 (9%)	3 (14%)		7 (11%)
Missing data	5	1		6
Time from HCT to relapse (months), median [IQR]	8.5 [3–16.8]	5 [3–11]	0.37	7 [3–15]
Time from relapse to blina (days), median [IQR]	19 [10–50]	22 [12.5–92]	0.27	22 [10–61.7]
Time from Blina to first DLI (days), median [IQR]		43.5 [35.2–73.8]		
Status at start of blina, *n* (%)			0.16	
CR	1 (2%)	2 (9%)		3 (4%)
Cytologic relapse	40 (80%)	14 (64%)		54 (75%)
Molecular only relapse	9 (18%)	6 (27%)		15 (21%)
Blina as first salvage therapy, *n* (%)	30 (67%)	10 (48%)	0.14	40 (61%)
Missing data	5	1		6
Nb of blina cycles, median [IQR]	2 [1-3]	3 [2–4]	0.01	2 [1-4]
Concomitant treatments				$n = 32$
Cytarabine-based chemotherapy				10 (31%)
Vincristine/Vindesine				12 (38%)
Clofarabine				2 (6%)
Tyrosine kinase inhibitors				9 (28%)
Local radiotherapy				2 (6%)

Blina blinatumomab, *DLI* donor lymphocyte infusion, *EM* extra-medullary relapse, *mo* months.

received also a DLI post blina and 1 patient received only 1 DLI 34 days before blina.

Treatments, other than blinatumomab, administered as post-salvage were heterogeneous. Ten patients received a cytarabine-based chemotherapy among which 6 were associated with methotrexate. Vincristine or Vindesine was administered in 12 patients either with steroids or with chemotherapy. Two patients received clofarabine. In Ph+ ALL, tyrosine kinase inhibitors (TKI), mostly ponatinib, were given in 9 patients. Two patients received local radiotherapy associated with steroids. After blina fifteen patients received a new HSCT (blina group = 9, blina-DLI group = 6) and 3 patients received CAR-T cells (blina group = 1, blina-DLI group = 2).

Outcomes after blina with/without DLI

The median follow-up was 38.6 [95% CI 31.3–41.9] months. It was 39.5 [95% CI 34.6–53.8] months in the blina group and 27.6 [95% CI 19.1–41.9] months in the blina-DLI group ($p = 0.03$). CR was obtained in 43/72 (60%) patients, including 25 (50%) in the blina group and 18 (82%) in the blina-DLI group including 6 patients achieving CR before DLI ($p = 0.018$). Of note, more than a half of patients in CR obtained this response after the first cycle (Table 3). Less than 25% of patients only obtained CR after cycle 3–5.

OS was 49.3% (37.3–60.3) at 1 year and 32 % (21.2–43.3) at 2 years (Table 4). PFS rates were 37.5% (26.1–48.9) and 23% (13.6–33.9), respectively. At 1 year, 59.4% (46.6–70.2) of patients relapsed or were in progression. At 2 years this rate accounted for 68.9% of patients (56–78.8). Non-relapse mortality was 3% (0.5–9.4) at 1 year and 8.1% (2.9–16.8) at 2 years.

DLI as time dependent variable was not significantly associated with outcome. For RI: HR = 0.66 (95%CI: 0.31–1.44) $p = 0.30$, for OS: HR = 0.64 (95% CI: 0.32–1.27) $p = 0.20$ and for EFS: HR = 0.73 (95% CI: 0.35–1.51) $p = 0.39$.

A landmark analysis was conducted on patients still alive at day 100 post blina ($n = 66$). Two years OS rates were 43% (20.2–64) in patients who received blina-DLI and 30.5% (17.7–44.2) in patients who received blina alone ($p = 0.31$) (Fig. 1).

In multivariate analysis, patient age and time from relapse to blina were not associated with outcomes (Table 5). MSD was associated with significant lower PFS ($p = 0.046$), with a trend for higher rates of relapse/progression ($p = 0.056$). A longer time from allo-HCT to relapse was associated with better CR rates ($p = 0.03$). Female sex was associated with better OS ($p = 0.042$).

Death was reported for 50/72 patients including 38 patients in the blina group and 12 patients in the blina-DLI group. Causes of death did not significantly differ between groups ($p = 0.76$). Relapse accounted for 71% of death (Table 3). Other causes were infection (16%), GVHD (8%) and hemorrhage (2%).

Adverse events and graft versus host disease after blina/blina-DLI treatment

Most frequent AE were hematological, neurological, and immunological, including cytokine release syndromes (CRS) (Table 5). AE rates were similar in the two groups except a low rate of neutropenia in the blina-DLI group (Table 6). Among the whole cohort, hematological AE included neutropenia (13%), anemia (6%) and thrombocytopenia (8%). Neurological events were reported for 14 (19%) patients and included headache, encephalopathy, and peripheral neuropathy. Six neurological AE were grade 3 or 4. In 14 patients (19%), immunological disorders were registered. Among them, 5 cases of CRS were diagnosed (7%) and 5 cases (7%) were registered as fever unrelated to infection and could be considered as grade 1 CRS. Only 1 case of CRS was more severe than grade 2. Seven (10%) patients experienced documented infection.

Three patients (6%) developed acute GVHD (aGVHD) after blina while 2 (9%) after blina-DLI (Table 6). All but one aGVHD cases

Table 3. Outcome after blina or blina-DLI.

Outcome	Blina alone ($n = 50$)	Blina - DLI ($n = 22$)	P	Overall ($n = 72$)
Follow-up, median [95% CI]	39.48 [34.6 – 53.8]	27.61 [19.1 – 41.9]	0.03	38.62 [31.3 – 41.9]
Best response, *n* (%)			0.018	
No CR obtained	25 (50%)	4 (18%)		29 (40%)
CR obtained	25 (50%)	18 (82%) (*)		43 (60%)
Date of CR, il CR is obtained, *n*				
After C1	13	10		23
After C2	5	4		9
After C3	2	2		4
After C4	0	1		1
After C5	3	1		4
Unknown	2	0		2
	Blina alone ($n = 38$)	Blina–DLI ($n = 12$)	*P*	Overall ($n = 50$)
Cause of death, *n* (%)			0.76	
Relapse	28 (74%)	7 (64%)		35 (71%)
GVHD	3 (8%)	1 (9%)		4 (8%)
Infection	5 (13%)	3 (27%)		8 (16%)
Hemorrhage	1 (3%)	0 (0%)		1 (2%)
Other	1 (3%)	0 (0%)		1 (2%)
Missing data	0	1		1

(*) including 6 patients achieving CR before DLI.
Blina blinatumomab, *CR* complete response, *DLI* donor lymphocyte infusion, *GVHD* graft versus host disease.

Table 4. CR, OS, PFS and RI / progression after blinatumomab.

	Patients (*)	1 year	2 years
CR	64	60.4 (46.6–71.7)	64.3 (50.5–75.2)
OS	72	49.3 (37.3–60.3)	32 (21.2–43.3)
PFS	68	37.5 (26.1–48.9)	23 (13.6–33.9)
RI / Progression (**)	68	59.4 (46.6–70.2)	68.9 (56–78.8)
NRM	68	3 (0.5–9.4)	8.1 (2.9–16.8)

CR complete response, *NRM* non-relapse mortality, *OS* overall survival, *PFS* progression free survival, *RI* relapse.
(*) Number of analyzed patients
(**) patients never in CR are considered as relapse at time of no CR

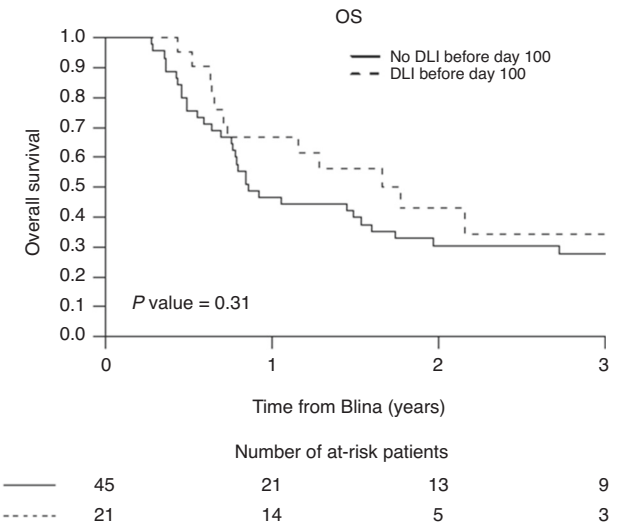

Fig. 1 Landmark analysis of overall survival. DLI donor lymphocyte infusion, OS overall survival.

were grade ≥ 2. Chronic GVHD (cGVHD) was diagnosed in 6 (12%) patients in the blina group, each in an extensive form. In the blina-DLI group, cGVHD accounted for 3 patients (14%) including 1 with extensive form.

DISCUSSION

Post-transplant relapse of B-cell acute lymphoblastic leukemia still represents today a critical condition associated with high mortality rates. In this retrospective study, we investigated the efficacy and safety of blinatumomab, a CD3-CD19 bispecific antibody, combined or not with DLI in this specific indication.

Firstly, we showed that the use of blina, even as single agent is associated with good response rates. Here, 60% of patients receiving blina or blina and DLI obtained CR as best response. Thirty-two patients (44%) obtained CR after 2 cycles of blina. These results are consistent with Stein et al. [16] who found a CR / CR with partial hematologic recovery of peripheral blood counts (CRh) rate of 45% after 2 cycles. Among the whole cohort presented here, OS was 49.3% and 32% at 1 and 2 years, respectively. In *Stein's* study, 1-year OS was 36%. Both of these results appear better than those obtained with chemo- or radiation-based salvage therapy even in association with second allo or DLI [6]. Thus, our data confirm that

Table 5. Univariate and multivariate analysis for CR rates, OS, PFS and relapse/progression rates.

	CR post blina		OS		PFS		RI/Progression	
	HR [95% CI]	P	HR [95% CI]	P	HR [95% CI]	P	HR [95% CI]	P
Univariate analysis								
DLI (*)	0.6 (0.3–1.3)	0.18	0.7 (0.3–1.3)	0.21	0.9 (0.5–1.6)	0.64	0.8 (0.4–1.7)	0.61
Multivariate analysis								
DLI (*)	0.5 (0.2–1.3)	0.15	0.6 (0.3–1.3)	0.20	0.7 (0.4–1.5)	0.39	0.7 (0.3–1.4)	0.30
Patient age (per 10 y)	0.9 (0.7–1.1)	0.34	1.1 (0.9–1.3)	0.44	1 (0.8–1.1)	0.54	0.9 (0.8–1.1)	0.38
Female vs male	0.9 (0.4–2.1)	0.89	0.5 (0.3–1)	0.042	0.6 (0.3–1.1)	0.10	0.6 (0.3–1.2)	0.15
Donor MSD vs other	1.5 (0.7–3.1)	0.34	1.4 (0.7–2.6)	0.28	1.9 (1–3.5)	0.046	1.9 (1–3.7)	0.056
Time from HCT to relapse (mo)	0.8 (0.7–1)	0.03	1 (0.8–1.2)	0.68	0.9 (0.8–1.1)	0.48	1 (0.8–1.1)	0.58
Time from relapse to Blina (mo)	1 (1–1)	0.33	1 (1–1)	0.22	1 (1–1)	0.22	1 (1–1)	0.17

CR complete response, *DLI* donor lymphocyte infusion, *HCT* hematopoietic stem cell transplantation, *HR* hazard ratio, *mo* months, *MSD* matched sibling donor, *OS* overall survival, *PFS* progression free survival, *RI* relapse, *y* years.
(*) Time dependent variable.

Table 6. Adverse events after blina or blina-DLI including GVHD.

Adverse events	Blina alone ($n = 50$)		Blina - DLI ($n = 22$)		Overall ($n = 72$)	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Hematological AEs, *n* (%)						
Neutropenia and febrile Neutropenia	8 (16)	8 (16)	1 (5)	1 (5)	9 (13)	9 (13)
Anemia	4 (8)	4 (8)	0 (0)	0 (0)	4 (6)	4 (6)
Thrombocytopenia	5 (10)	5 (10)	1 (5)	1 (5)	6 (8)	6 (8)
Immunological disorders, *n* (%)						
Fever unrelated to infection	5 (10)	0 (0)	3 (14)	0 (0)	8 (11)	0 (0)
Cytokine release syndrome	5 (10)	1 (2)	1 (5)	0 (0)	6 (8)	1 (1)
Neurological AEs, *n* (%)						
Headache	3 (6)	0 (0)	1 (5)	0 (0)	4 (6)	0 (0)
Encephalopathy	2 (4)	1 (2)	1 (5)	1 (5)	3 (4)	2 (3)
Peripheral neuropathy	3 (6)	2 (4)	0 (0)	0 (0)	3 (4)	2 (3)
Non specified/others	2 (4)	1 (2)	2 (9)	1 (5)	4 (6)	2 (3)
Other AEs, *n* (%)						
Fatigue	1 (2)	1 (2)	1 (5)	1 (5)	2 (3)	2 (3)
Tumor lysis syndrome	1 (2)	1 (2)	0 (0)	0 (0)	1 (1)	1 (1)
Hepatobiliary disorders	2 (4)	1 (2)	1 (5)	1 (5)	3 (4)	2 (3)
Gastro-intestinal disorders	3 (6)	1 (2)	0 (0)	0 (0)	3 (4)	1 (1)
Including pancreatitis	1 (2)	1 (2)	0 (0)	0 (0)	1 (1)	1 (1)
Infectious disease	5 (10)	5 (10)	2 (9)	2 (9)	7 (10)	7 (10)
AEs related to material	2 (4)	0 (0)	0 (0)	0 (0)	2 (3)	0 (0)
Splenic infarction	1 (2)	1 (2)	0 (0)	0 (0)	1 (1)	1 (1)
GVHD	Blina alone ($n = 50$)		Blina–DLI ($n = 22$)		Overall ($n = 72$)	
Acute GVHD, *n* (%)	All grades	Grade ≥2	All grades	Grade ≥2	All grades	Grade ≥2
	3 (6)	2 (4)	2 (9)	2 (9)	5 (7)	4 (6)
Chronic GVHD, *n* (%)	All grades	Extensive	All grades	Extensive	All grades	Extensive
	6 (12)	6 (12)	3 (14)	1 (5)	9 (13)	7 (10)

AEs adverse events, *DLI* donor lymphocyte infusion, *GVHD* graft versus host disease.

blina represents an effective option for salvage therapy after post-transplant relapse.

Secondly, we questioned the possibly of a synergy between blina and DLI. Indeed, blina is a T cell engager. By binding patient's CD3-positive cytotoxic T cells, this bi-specific antibody allows them to recognize and finally eliminate CD19-positive ALL blasts [22–24]. Consistent to that, baseline percentage of CD3 + CD8 + effector T cells has been shown to predict response to blina in refractory or relapsed B-ALL patients [25]. Thus, effectiveness of blina probably depends on T cells recovery after transplant. As patients relapsing after transplant present a poorer immune reconstitution [26–28], optimizing this reconstitution is probably a key to enhance blina efficacy.

Here, the combination of DLI to blina did not seem to enhance its efficacy. Although, 81.8% of patients in the blina-DLI group obtained CR, DLI considered as a time dependent variable was not statistically associated with OS, PFS or relapse rates in multivariate analysis.

Only a few cases of such combination have been reported in the literature. *Durer et al.*, described a 51-year-old woman who received 4 cycles of blina and 3 DLI. Because of an extramedullary associated disease, she also received subsequent chemotherapy [29]. This combined treatment conferred her more than 14 months of complete remission. *Ueda et al.*, reported the outcome of 4 patients treated concomitantly with blina and DLI. Two of them were still in complete remission after a respective follow up of 7

and 13 months [30]. In the same way, Papayannidis et al., reported 8 patients receiving Inotuzumab and DLI for post-transplant relapse of B-ALL. Among them 6 obtained complete response with negative MRD. Median RFS was 12.0 months (IQR 8.2–26.7), and median OS was not reached in this study [31].

Our study did not confirm a synergy between drugs. Nevertheless, it was conducted in a real-life manner and reflects various and inhomogeneous practices. Administration of DLI concomitantly to blina infusion is probably a clue to obtain synergy. Indeed, blina has a short elimination half-life [32].

Thirdly, administration of blina in combination or not with DLI appears to be safe. Indeed, the most common AE were hematological, neurological, infectious and the induction of CRS. These AE are those classically reported in phase 2 [33–35] and phase 3 [15] trials evaluating blina in relapsed or refractory B-cell ALL. No grade 5 toxicity has been reported. These AE are also consistent with those described in Stein's study [16]. Considering GVHD, only a few data support its induction by blinatumomab. Khan and Gul reported a 61-year-old woman with no history of GVHD developing gut and liver GVHD after 2 cycles of blina. In the aftermath, she obtained a complete remission and a 100% positive donor chimerism [36]. In Stein et al., 7 patients in 64 experienced GVHD after post-transplant blina [16]. This rate was substantially lower than in our study. However, the study design in *Stein's* trial systematically excluded patients with active GVHD or receiving systemic treatment for GVHD prior to blina and could explain the difference.

Interestingly, we did not observe any strong excess of toxicity in the blina-DLI group. Both aGVHD and extensive cGVHD rates were also low in the combined treatment group. Thus, considering toxicities, combination appears feasible.

In recent years, treatment of relapse of ALL dramatically changed thanks to several developments. Among them, CAR-T cell therapy is an exciting approach. Tisagenlecleucel shows remarkable efficacy in pediatric patients and young adults in clinical trials [37, 38]. After the ZUMA-3 phase 2 trial [39], brexucabtagene autoleucel (KTE-X19) also obtained FDA approval The broad use of CAR-T cells in adults is impeded by toxicities such as cytokine release syndrome or Imune effector cell-associated neurotoxicity syndrome (ICANS) [40]. Clinicians must also think about economical and organizational issues related to this procedure [41]. It is critical to consider that CAR-T cells are manufacturing products engineered for each individual patient. Thus, obtaining CAR-T cells depend on the quality of leukapheresis. This also induces a non-reducible manufacturing time which could be detrimental for patients and even result in death. For instance, in the ZUMA-3 phase 2 trial, the median time from leukapheresis to CAR-T manufacturing release was 13 days [39]. In 71 enrolled patients, only 55 finally received the KTE-X19 CAR T cells. Thus, blina represents an interesting alternative in a subset of transplant patients who failed leukapheresis or are not responders to bridging therapy. As blina is an "off the shelf" therapy, its use appears easier and faster.

This study presents some limitations. Firstly, the low GVHD rates found in the DLI group must be mitigated by the fact that physicians preferentially proposed DLI to patients who did not show signs of GVHD or experienced severe GVHD in the past. Indeed, only 27% of patients presented acute GVDH before treatment in the blina-DLI group versus 44% in the blina group.

Secondly, due to its retrospective design we did not control treatment given prior to, after or in parallel with blina and DLI. This could lead to bias. However, due to the severity of post-transplant relapses, combining therapies are probably needed. For instance, the association of TKI in case of Ph-positive or Ph-like ALL is attractive and should be considered [42, 43].

Thirdly, data were lacking about minimal residual disease (MRD) assessment after blina treatment.

Despite the limitations presented above, this study is one of the largest focusing on the use of blinatumomab in combination with DLI in B-ALL patients relapsing after allo-HCT. Its multicentric approach offers us a more representative picture in real life.

Prospective studies are needed to determine if better combination modalities between blina and DLI could enhance efficiency. A cycle of blina consisted of 28 days of continuous intravenous infusion followed by 14 days off. We suggest that DLI could be infused at the end of this period just before blina re-administration in order to enhance their synergy. According to this scheme of administration, DLI will be infused after the end of the first cycle of blina which is at higher risk of toxicities such as CRS. Thus, managing toxicities will be easier for physicians. As another approach that could be of great interest would be to administer blinatumomab in prophylaxis. Gaballa et al., have recently reported a phase 2 study showing the feasibility of 4 cycles of blinatumomab every 3 months in the post-transplant setting as maintenance in B-ALL patients [44]. Prospective and randomized studies are needed to evaluate the efficacy of this strategy that could also be combined with DLI. Considering only relapsed patients were included in our study, this late strategy has not been addressed here.

In conclusion, the use of blinatumomab in post-transplant relapse of B-ALL is safe and effective. Adding DLI between 1 month before and 100 days after start of blina does not seem to improve outcomes or toxicities in our study.

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AUTHOR CONTRIBUTIONS

PCha, EB, AP, MLa and IYA designed the study. AP and MLa performed statistical analysis. PCha, EB, AP, MLa and IYA analyzed data. PCha and EB wrote the manuscript. All authors collected data and reviewed the manuscript.

COMPETING INTERESTS

PChe has received honoraria from Amgen. The other authors declare no conflict of interest relative to this work.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Paul Chauvet or Eolia Brissot.