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Combined adoptive immunotherapy with Blinatumomab and donor lymphocyte infusions in children with relapsed/refractory B-ALL after allogeneic stem cells transplantation

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Summary

Allo-HSCT is potential curative option for high-risk pediatric B-cell acute leukemia (B-ALL), nevertheless about 30-70% of patients relapsed after allo-HSCT. Patients with relapsed/refractory (r/r) B-ALL have a dismal prognosis with 3-year probability overall survival (OS) about 20%. In this study we firstly appreciated efficacy and safety of combined adoptive immunotherapy with bispecific T-cell engager Blinatumomab and donor lymphocyte infusions (DLI) for 17 children underwent allo-HSCT and having relapse or minimal residual disease (MRD) after that. Fifteen (88%) of patients achieved a complete remission within the first 2 cycles of treatment with blinatumomab and DLI. The median relapse-free survival was 9.1 months (95% CI, 3.0 to 37.2 months) in patients who achieved CR, with the median duration follow up 13,3 months (95% CI, 10.0 to 30.3 months). The median overall survival for all patients was not reached at a median follow-up of 13.3 months (95% CI, 8.8 to 27.4 months). The Kaplan-Meier estimate overall survival was 76.5% (95% CI, 44%-92%) at a median follow-up time 13,3 months. Three children (18%) experienced drug-related adverse events grade 3 and two children (12%) had clinically significant induced "graft-versus-host disease" (GVHD). There were no fatal cases due to the therapy. Further immunotherapy options for r/r pediatric ALL may include repeated courses of combined adoptive immunotherapy, monotherapy of escalated DLI, chimeric antigen receptor T-cell therapies, checkpoint inhibitors or undergo second allo-HSCT.

Keywords

B-cell acute leukemia, children, relapse, allo-HSCT, blinatumomab, donor lymphocyte infusions.

Introduction

Acute lymphoblastic leukemia (ALL) is one of the most spread pediatric cancers. With improvements of protocols for new diagnosed ALL nowadays 5-year survival achieves approximately 80-90% for these children [1]. However, patients with primary chemoresistance disease or relapse have a dismal prognosis with 5-year OS in first relapse of about 50% [2]. Allogeneic hematopoietic stem cells transplantation (allo-HSCT) has become a standard treatment for high-risk pediatric ALL. Many conditions affect the results of allo-HSCT: age, HLA-incompatibility between the donor and recipient, conditioning regimens, status of disease at the moment of allo-HSCT, persistence of minimal residual disease (MRD) and other [3]. Incidence of relapse after allo-HSCT reaches 70% in patients without remission at the

moment of allo-HSCT compare with patients having remission (up to 35% of relapses). Patients with clinic of acute or chronic GVHD have a benefit in OS due to proceeding graft-versus-leukemia reaction [4, 5]. Patients with relapsed/refractory (r/r) disease after allo-HSCT have a poor prognosis with 3-year probability OS about 20% using different salvage option [6]. There are no standard recommendations for this group of patients. Clinical approaches include cytoreductive chemotherapy, target drugs, donor lymphocyte infusion (DLI), CAR-T cells, monoclonal antibody or palliative care. Treatment choices are individualized and depend on somatic status of patients, time of relapse, type of relapse and immune response.

Because most ALL cells in relapse have chemoresistance and get ability to escape the immune-suppressive tumor response conventional chemo-drug induce very short remission and not effective in long time survival.

DLI is a form of adoptive immunotherapy, which mechanism of action based on induction of graft-versus-leukemia (GVL) effect. Patients with ALL in general are less sensitive for immunotherapy, than AML patients, and other reasons of weak response to DLI is immune resistance by immune checkpoint expression, tumor microenvironment or loss of recipient-specific HLA genes [7, 8].

However, the study Nicole Liberio et al. [9] showed, that DLIs could promote durable survival after allo-HSCT in childhood ALL cohort. Moreover, the results of DLI as a therapy for relapsed acute leukemia may be shown comparable to second allo-HSCT [10].

Blinatumomab is a bispecific T-cell engager (BiTE) with two different single-chain Fv fragments binding T-cell CD3 and B-cell CD19 antigens. According to previous studies, blinatumomab has been demonstrated high efficacy in pediatric r/r B-ALL with a good tolerable safety profile. Response rate may reach 90% depending on tumor burden with a long median relapse-free survival (RFS) [11]. Low toxicity allows using this drug after allo-HSCT with comparable results [12, 13].

In study Hengwei Wu et al., [14] blinatumomab showed efficacy in patients undergoing HLA loss relapse after haplo-HSCT. Supposed, that blinatumomab may restore GVL effect.

So, we expect blinatumomab may not only reduce tumor cells, but also make stronger immune pressure for action of DLI.

Here we present first single-center experience of using immunotherapy with Blinatumomab and DLI in 17 children with refractory/relapsed (r/r) CD19+ B-ALL after allo-HSCT.

Patients and methods

We enrolled in this prospective study 17 B-ALL patients with the median age 10 years (8 months-18 years), who were treated by immunotherapy with Blinatumomab and DLI after allo-HSCT. Among them 3 patients (18%) had infant ALL with rearrangement *KMT2A*. All patients underwent allo-HSCT at RM Gorbacheva Research Institute within a period from 2012 to 2021. Eleven patients (65%) had received a myeloablative conditioning regimen (MAC), including 8 (47%) Bu-based (12-16 mg/kg) conditioning regimen, 2 GIAC [busulfan 3 mg/kg, cyclophosphamide 100 mg/kg, lomustine 120 mg/m^2, cytarabine 6000 mg/m^2] protocol (12%) and one Treosulfan+Fludarabin+Thiotepa followed by TCR αβ+/CD19+ cell depletion. Six patients (35%) had received a reduced-intensity conditioning regimen (RIC) Fludarabin 150mg/m^2 and Melphalan 140 mg/m^2. Most children (n=13, 76%) had haploidentical donor, three (18%) patients had matched unrelated donor and one patient had matched related donor. Sixteen (94%) were given regimen of prophylaxis GVHD with cyclophosphamide (PtCy) 50 mg/kg on D+3, D+4, one patient was given immunosuppressive therapy with Rituximab, Tocilizumab, Abatacept after transplantation with TCR αβ+/CD19+ cell depletion. Engraftment with full donor chimerism was confirmed in all analyzed patients. History of acute GVHD of skin grade II after allo-HSCT was observed in 1 (6%) child, history of chronic GVHD of skin mild grade – in 2 children (12%). Disease status before starting of blinatumomab was post-transplant bone marrow relapse in 11 (65%) patients, MRD in 6 (35%) patients. Extramedullary lesions before blinatumomab therapy were observed in 4 patients (24%): 3 patients with involvement of central neural system (CNS) and 1 patient with testicular involvement. Early bone marrow relapse/MRD >10^{-4} leukemic blasts of leukemia (up to one year after allo-HSCT) developed in 9 patients (53%). BM relapse occurred up to D+100 in 6 (35%) patients. Five patients (29%) with relapse of the disease had received salvage fludarabine-containing chemotherapy before treatment with blinatumomab. Four patients (24%) had response as blast cell reduction after salvage chemotherapy. Patients with MRD had full donor chimerism before starting blinatumomab and DLI, among patients with relapse 10/11 had chimerism more 50%.

Primary endpoints of the study were overall response rate, relapse-free survival (RFS), overall survival (OS). Overall response included morphologic CR (<5% blasts) and MRD response (<10^{-4} leukemic blasts by flow cytometry or polymerase chain reaction) within the first 2 cycles of treatment with blinatumomab and DLI. RFS and OS was calculated from the start of blinatumomab treatment to time of relapse, death, consequently.

Relapse was determined as bone marrow recurrence of disease or extramedullary lesions. Secondary endpoints included frequency of induced acute and chronic GVHD after immunotherapy, grade 3 or higher treatment-related adverse events by NCI CTCAE 5.0, duration of bone marrow response (DOR). DOR was defined as time from initial response to bone marrow relapse, death. Patients alive were censored on the last documented visit date or last contact date.

Relapse-free survival and overall survival are described with Kaplan-Meier with 95% CI estimates. Statistical analysis was performed using IBM SPSS Statistics v 26 and Free statistical software: EZR (Easy R).

Results

Median time from allo-HSCT to blinatumomab therapy was 12 months (range, 2 months – 43 months). Blinatumomab (5-15 μg/m^2 *per* day) was administered as a 4-week

Table 1. Demographic Data and Baseline Disease Characteristics (n=17)

Characteristic	Value
Male sex, n (%)	13 (76)
Age, yr, median (range)	10 (0.7-18)
Donor type, n (%):	
Haploidentical	13 (76)
Sibling	1 (6)
Matched Unrelated	3 (18)
Conditioning regimens, n (%):	
Myeloablative	11 (65)
Reduced intensity	6 (35)
Cyclophosphamide in GVHD prophylaxis, n (%)	16 (94)
Rituximab, Tocilizumab, Abatacept in GVHD prophylaxis, n (%)	1 (6)
Source of stem cells, n (%):	
Bone marrow	15 (88)
Peripheral blood	2 (12)
Disease status before allo-HSCT:	
MRD negative 1st–2nd remission	7 (41)
MRD positive 1st–2nd remission	2 (12)
Relapse/Progression	8 (47)
History of GVHD, n (%)	
Chronic mild grade	2 (12)
Acute II grade	1 (6)
Disease status before blinatumomab:	
Minimal residual disease	6 (35)
Bone marrow relapse	11 (65)
Extramedullary lesions	4 (24)
Baseline bone marrow blast before blinatumomab, n (%)	
<20%	12 (71)
>=20%	4 (24)
Not available	1 (6)
Number of relapse after allo-HSCT n (%):	
1	14 (82)
2	3 (18)
Median Time from allo-HSCT to developing of MRD/relapse, months (range)	10 (1-30)
Fludarabine-containing chemotherapy before treatment with blinatumomab, n (%)	5 (29)
Response after cytoreductive chemotherapy	
Blast cell reduction	4 (24)
Progression	1 (6)

induction cycle. Patients received up to 3 courses of blinatumomab with the median 1 course. First DLI was mostly given after starting blinatumomab course 1 (ranged from course 1 to course 2) on median day 32 therapy (1-123). Seven patients got first dose of DLI at the moment blinatumomab administration, 3 patients – in several days after finishing blinatumomab administration and seven patients – in 1-3 months after finishing blinatumomab at CR. Total, from 1 to 4 DLI were performed at follow up, doses varied between 1×10^5 and 6×10^7 CD3+/kg. Summary median dose of DLI during the combined therapy was 1.7×10^6 CD3+/kg (range, 1×10^5-6×10^7).

Efficacy

The median overall survival for all patients was not reached at a median follow-up of 13.3 months (95% CI, 8.8 to 27.4 months); four (24%) died from progression of leukemia. The Kaplan-Meier estimate overall survival was 76.5% (95% CI, 44%-92%) at a median follow-up time (Fig. 1).

Fifteen (88%) of patients achieved a CR within the first 2 cycles of treatment with blinatumomab +DLI, among them 14 (82%) had MRD negative CR. Median duration of bone marrow response was 7 months (range, 1 to 55.0 months). The median relapse-free survival was 9.1 months (95% CI, 3.0

to 37.2 months) in patients who achieved CR, with the median duration follow up 13,3 months (95% CI, 10.0 to 30.3 months); 10 (67%) patients relapsed, including bone marrow relapse in 4 patients (27%), combined (BM+CNS/bones/parenchymal organs) in 3 (18%) and isolated extramedullary relapse (CNS in 2 and soft tissues in 1) in three (18%) patients (Fig. 2). One patient underwent successful subsequent allo-HSCT after relapse and still alive in MRD negative CR.

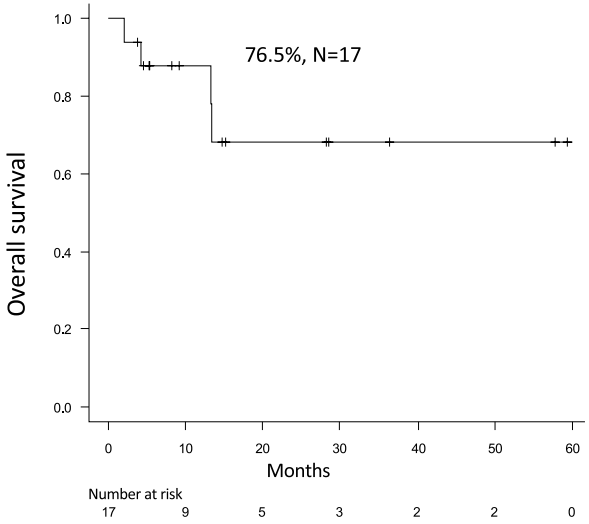

Figure 1. Overall survival in all B-ALL patients

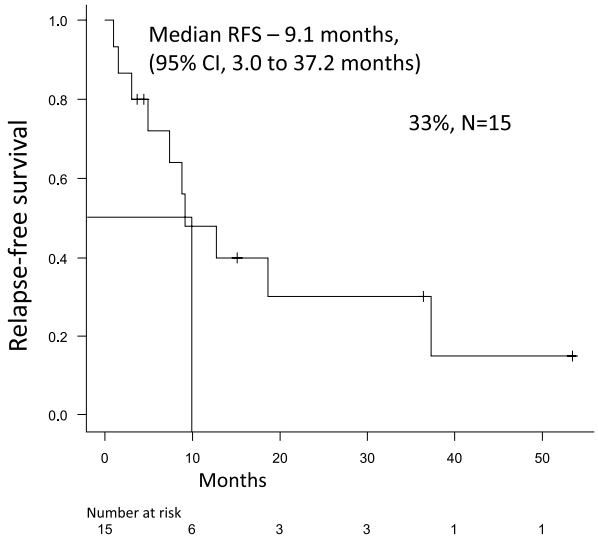

Figure 2. Relapse-free survival in B-ALL pediatric patients responding to the therapy

Safety

Three children (18%) experienced drug-related adverse events grade 3. One patient had seizure and required transient blinatumomab discontinuation, 1 patient had generalized cytomegalovirus (CMV) infection with involvement of blood, lung and urinary tract, 2 patients had infectious enterocolitis grade 3 (*Clostridia*, *Serratia spp.*, CMV). There were no observed cytokine release events, grade 4 or fatal reactions.

There were no fatal acute and chronic GVHD after therapy by blinatumomab and DLI. But, one patient (6%) experienced induced acute GVHD of skin and gastrointestinal tract grade 3 after combined immunotherapy. Three children (18%) had chronic GVHD. One patient had classical severe GVHD of skin, gastrointestinal tract and liver after acute GVHD grade 3. One patient had classical mild GVHD of skin and oral mucosa. One patient had "overlap" moderate GVHD of skin and eyes. One patient with history of mild chronic GVHD developed mild chronic GVHD during combined immunotherapy. GVHD was induced in one month after DLI administration in all children. Two patients with chronic GVHD (moderate and severe form) received immunosuppressive therapy (steroids, tacrolimus/sirolimus and ruxolitinib) with success control of symptoms. DLI were discontinued after development of moderate and severe chronic GVHD. Two of 3 patients with chronic GVHD remain in long term CR during 12 and 35 months with good quality of life. Clinical outcomes are shown in Table 2 and Table 3.

Table 2. Clinical outcomes and complications in the B-ALL patients

Outcome (n=17)	Value
CR in first 2 cycles), n (%)	15 (88)
MRD response	14 (82)
Adverse event grade 3:	3 (18)
Seizure	1 (6)
cytomegalovirus infection	1 (6)
enterocolitis	2 (12)
Acute GVHD grade 3	1 (6)
Chronic GVHD:	3 (18)
Mild	1 (6)
Moderate	1 (6)
Severe	1 (6)

Discussion

Allo-HSCT may be a curative treatment option for high-risk ALL, however, a portion of patients become refractory or relapse after allo-HSCT with the rate between 30% and 70%. Progressive leukemia remains the main cause of mortality after allo-HSCT.

In our study we have demonstrated results of adoptive immunotherapy based on combination bispecific T cell engager (BiTE) blinatumomab and DLI for salvage group of 17 pediatric B-ALL, including 3 infant ALL with rearrangement KMT2A. This combination is promising with overall rate response (88%) both in patients with persistence MRD and bone marrow relapse. Incidence complete response was higher, than that observed in patients who receive mono-DLI (43%) [9]. It is known that tumor burden has great importance before immunotherapy, so cytoreductive chemotherapy was administered previous in 5 (29%) relapsed patients [12]. One patient with early 4th relapse and large tumor burden didn't receive cytoreductive therapy and progressed during immunotherapy.

Table 3. Treatment details in the distinct clinical B-ALL cases

№	Age, years	Status of disease before blincito+DLI	Months after allo-HSCT	Chemo-therapy before blincito+ DLI	First dose DLI, CD3+/kg	Best Response	GVHD	DOR in BM, months	Relapse	Follow up
Blinatumomab+DLI after cytoreductive chemotherapy for relapse										
1	10	Relapse	6	FLAG	5×10^5	CR	No	1	Bone marrow	Alive after second allo-HSCT
2	9	Relapse	31	FLAG	1×10^5	CR	No	55	Extramedulllar	Alive
3	13	Relapse	19	F1	1×10^6	CR	No	16	Combined	Alive
4	16	Relapse	31	FLAIDA	5×10^5	CR	No	52	No	Alive
5	0.7	Relapse	1	FLAIDA	1×10^5	Molecular MRD	No	7	Extramedulllar	Alive
Blinatumomab +DLI without cytoreductive chemotherapy for relapse										
6	8	Relapse	2	No	1×10^6	Pro-gressive disease	No	0		Death
7	18	Relapse	1	No	1×10^6	CR	Acute and Chronic severe	11	Combined	Death
8	11	Relapse	23	No	1×10^6	CR	No	6	Bone marrow	Alive
9	8	Relapse	8	No	6×10^7	CR	Chronic moderate	12	No	Alive
10	4	Relapse	3	No	1×10^6	CR	No	3.5	No	Alive
11	10	Relapse	15	No	1×10^5	CR	No	3	No	Alive
Blinatumomab +DLI without cytoreductive chemotherapy for MRD										
12	16	MRD	26	No	1×10^5	CR	Chronic mild	35	No	Alive
13	0.8	MRD	1	No	1×10^5	CR	No	8	Bone marrow	Death
14	9	MRD	1	No	1×10^6	Progressive disease	No	0		Death
15	10	MRD	12	No	5×10^7	CR	No	8	Combined	Alive
16	11	MRD	28	No	1×10^7	CR	No	3	Bone marrow	Alive
17	1	MRD	6	No	1×10^6	CR	No	27	Extramedulllar	Alive

We have found good short-term toxicity profile of this therapy without the necessary for complete withdrawal of therapy due to adverse events. Infectious complications grade 3, observed in 3 children, could be associated also with pretreatment and absent of full immunological reconstitution after allo-HSCT.

The most common complication after DLI is the induction of acute and chronic GVHD, which develops general in 40-50% of patients. However, the use of PtCy may reduce the risk of developing induced GVHD [15]. The occurrence of chronic GVHD after DLI is considered to be a favorable factor associated with a reduced risk of recurrence and long-term disease-free survival [16, 17, 18, 19, 20, 21].

While the most lymphocyte infusions were haploidentical, the incidence of GVHD was low (24%), that similar with early published study, where haplo-DLI was used for relapse treatment after T cell replete bone marrow transplantation with post-transplantation cyclophosphamide. [15]. Two of 3 patients with GVHD remains in long CR during 12 and 35 months.

Systematic review reported summarized data about concomitant use of blinatumomab and DLI for post-transplant relapsed CD19 positive ALL on 15 adult patients according 2 studies. Before starting blinatumomab therapy, 12 patients had post-transplant bone marrow relapse, 1 patient had an extramedullary relapse, and 2 patients had a MRD without marrow relapse. DLI was mostly given with blinatumomab during cycle 3 (ranged from cycle 2 to cycle 4). Complete remission (CR) with MRD negative status was achieved after 2 cycles of blinatumomab in 3 patients, 2 of them

remained in CR for 7 and 13 months. Ten patients showed RR of 70%. One patient developed grade II aGVHD after the combination therapy, Grade 3 late-onset acute skin and gut GVHD were reported in one patient. One patient continued progression of extramedullary disease, 1 patient died to extramedullary and hematologic relapse 12 months after blinatumomab initiation [22, 23].

In our study totally 6 (35%) patients developed relapse with extramedullary involvement, 2 of them had extramedullary before immunotherapy. Five patients with extramedullary involvement are still alive after relapse, 3 of them continue the treatment.

Unfortunately, despite high response rate and a durable remission in our work relapse of disease occurred in 67% of patients. These patients need in continuation of escalated DLI with/without courses of blinatumomab should be considered to control the disease, if there are no signs of clinically significant GVHD.

Further alternative approaches to overcome immune resistance may include chimeric antigen receptor T-cell therapies, checkpoint inhibitors or undergo second allo-HSCT [24, 25, 26, 27].

In the era of immunotherapy, future challenges and goals will be based on understanding the mechanisms of immune evasion by leukemia cells for developing novel therapeutic strategies.

Conclusion

Combination adoptive immunotherapy of blinatumomab and DLI is effective and can induce long-term bone marrow remissions in some relapsed pediatric CD19+ B-ALL after allo-HSCT.

1. Blinatumomab+DLI has a low toxicity profile, low incidence of GVHD and is well tolerated even by young children after haplo-HSCT.

2. The use of immunotherapy after cytoreductive chemotherapy is preferable in patients with extensive bone marrow relapse.

3. For maintaining of durable remission responded patients are needed further treatment.

Conflict of interest

None declared.

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Комбинированная адоптивная иммунотерапия с применением блинатумомаба и инфузий донорских лимфоцитов у детей с рецидивирующим/рефрактерным течением В-ОЛЛ после алло-ТГСК

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Резюме

Алло-ТГСК является потенциально излечивающим методом терапии детей с В лимфобластным лейкозом (В-ОЛЛ) группы высокого риска. Тем не менее, примерно у 30-70% пациентов возникает рецидив после алло-ТГСК. Пациенты с рецидивирующим/рефрактерным течением В-ОЛЛ имеют неблагоприятный прогноз с 3-летней общей выживаемостью (ОВ) около 20%. В этом исследовании мы впервые оценили эффективность и безопасность комбинированной адоптивной иммунотерапии биспецифическим активатором Т-клеток блинатумомабом и инфузиями донорских лимфоцитов (ИДЛ) у 17 детей, перенесших алло-ТГСК и имевших после этого рецидив или персистенцию минимальной остаточной болезни. Пятнадцать (88%) пациентов достигли ремиссии в течение первых 2 циклов лечения блинатумомабом +ИДЛ. Медиана безрецидивной выживаемости составила 9,1 мес (95% ДИ, от 3,0 до 37,2 мес.) у пациентов, достигших ответа, с медианой наблюдения 13,3 мес. (95% ДИ, 10,0-30,3 мес.). Медиана ОВ для всех пациентов не была достигнута при медиане наблюдения 13,3 месяца (95% ДИ, от 8,8 до 27,4 месяцев). ОВ по Каплану-Мейеру составила 76,5% (95% ДИ, 44-92%) при медиане наблюдения 13,3 месяца. Трое детей (18%) развили нежелательные явления 3-й степени тяжести, связанные с введением препарата, и двое детей (12%) имели клинически значимую индуцированную реакцию «трансплантат против хозяина» (РТПХ). Летальных случаев, связанных с терапией, отмечено не было. Дальнейшие варианты иммунотерапии детей с рецидивирующим течением В-ОЛЛ могут включать продолжение курсов комбинированной адоптивной иммунотерапии, монотерапию ИДЛ в эскалированных дозах, терапию Т-клетками с антигенным химерным рецептором, ингибиторами контрольных точек, а также проведение повторной алло-ТГСК.

Ключевые слова

В-клеточный острый лимфобластный лейкоз, дети, рецидив, алло-ТГСК, блинатумомаб, инфузии донорских лимфоцитов.