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Features of response to blinatumomab and inotuzumab ozogamicin therapy in patients with relapse/refractory B-cells acute lymphoblastic leukemia in real clinical practice

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Summary

Allogeneic hematopoietic stem cell transplantation is an effective method to cure patients with relapse/refractory (r/r) B-cell acute lymphoblastic leukemia, and deep remission without minimal residual disease is the key factor for the favorable outcome. Monoclonal antibodies (bispecific T-cells engager and conjugates) are the promising option to achieve complete remission in these patients. Our aim was to summarize the results of a single-center non-randomized study in order to investigate in real clinical practice the results of treatment with blinatumomab and inotuzumab ozogamicin in children and adults in heterogeneous cohort of r/r B- ALL.

Results of the single-center non-randomized pilot study in real clinical practice showed high response rate in heterogeneous cohort of r/r B- ALL. The study group included 182 patients with r/r B-ALL, their age was from one to 72 years old. 128 patients were treated with blinatumomab, 54 patients received inotuzumab ozogamicin. Overall response was high in both groups, 96 (75%) and 44 (82%). The major predictors of response were adult age (OR= 3.819; 95% CI, 1.744-8.223; p=0.001) and clinical indications, i.e., active disease or measurable residual disease (OR= 0.018; 95% CI, 0.153-0.841; p=0.01). The other clinical or disease parameters had no significant impact on response.

Keywords

B-cell acute lymphoblastic leukemia, relapse/refractory, monoclonal antibodies, blinatumomab, inotuzumab ozogamicin, overall response.

Introduction

In recent years, the outcome of patients with B-cell acute lymphoblastic leukemia (B-ALL) has improved dramatically due to the use of modern chemotherapy regimens. In children with B- ALL cure rate varies within 70%-80%, while in adults – within 15%-40% [1, 2] However, primary resistance and relapses that do occur in 15%-25% of children, and in 50%-70% of adults, and significantly impact survival [3, 4]. In relapsed patients, the prognosis is adverse and after each relapse, the outcome is deteriorating. In case of third and further relapses the probability to achieve remission by salvage high-dose chemotherapy is decreasing. In addition, when using intensive chemotherapy, commutative toxicity is

accumulating which is an additional risk factor for increasing the incidence of non-relapse mortality during allogeneic hematopoietic stem cells transplantation (allo-HSCT) [5, 6, 7]. The depth of the response is another factor which impacts the allo-HSCT efficacy, and salvage chemotherapy rarely induces molecular remissions [7, 8, 9, 10].

The emergency of different monoclonal antibodies (BITE, conjugated) has significantly expanded our options for treatment of the patients with relapsed/refractory (r/r) B-cell ALL.

Currently blinatumomab, a bispecific T-cells engager monoclonal antibody (anti-CD19), and inotusumab ozogamicin, a conjugate monoclonal antibody (anti-CD22), are the most promising in treatment of r/r B-ALL in children and adults, which has been shown in a large number of studies [11, 12, 13, 14, 15, 16]. Their pharmacokinetics and pharmacodynamics have been well studied to date. But there are still many unresolved questions concerning use of these monoclonal antibodies in real clinical practice. Various pilot studies and randomized clinical trials have shown the advantages of blinatumomab and inotuzumab over standard and salvage chemotherapy [17, 18].

Our aim was to summarize the results of a single-center non-randomized study in order to investigate in real clinical practice the results of treatment with blinatumomab and inotuzumab ozogamicin in children and adults in heterogeneous cohort of r/r B-ALL.

Patients and methods

The study included patients, both children and adults, with different types of r/r B-ALL who were treated with monoclonal antibodies – blinatumomab and inotuzumab ozogamicin in real clinical setting. The patients were treated in Raisa Gorbacheva Memorial Institute of Pediatric Oncology, Hematology and Transplantation, Pavlov University, Saint-Petersburg from April 2015 to October 2019. All the patients gave informed consent for the treatment, each case was approved by the Russian Ministry of Health for individual use of investigational product.

The group of patients in our study was heterogenous for different parameters. The heterogeneity was due to genetic markers of r/r B-ALL patients, age differences, as well as different types of relapses, previous therapy and clinical state of the disease (hematological or molecular relapses) at the moment of starting therapy by blinatumomab or inotuzumab (Table 1). Hematological relapse (HR) was determined in cases with more than 5% blasts in bone marrow.

Molecular relapse (MR) was diagnosed if minimal reduced disease (MRD) was defined as presence of leukemia blasts not detectable by microscope, being, however, revealed by mutation-specific polymerase chain reaction (PCR) or flow cytometry, if the relevant result was >1 malignant cell per 10^{-4} normal counterparts.

The patients received blinatumomab by continuous intravenous infusions. One course included 4-week treatment followed by 2-weeks pause in treatment. The doses were as follows: in adult patients with hematologic relapse and children with hematologic and molecular relapses weighing >45 kg, at the dose of 9 mcg/d for the first week in cycle, and 28 mcg/d over the remaining 3 weeks. The patients with body mass of <45 kg received 5 mcg/m^2/d during first week, and 15 mcg/m^2/d over following 3 weeks. Adult patients with molecular relapses received 15 mcg/m^2/d during 4 weeks. Inotuzumab ozogamycin was administered in adult and children groups at the same dosage: one cycle consisted of 3 dose regimens, i.e., 0.8 mg/m^2 on week 1, and 0.5 mg/m^2 on week 2 and week 3.

Patients with r/r Ph-positive B-ALL were treated with combination of blinatumomab or inotuzumab with different tyrosine kinase inhibitors at recommended doses administered during therapeutic cycles. Next types of response were registered: complete remission without MRD, i.e., molecular remission, and complete remission with MRD termed as hematological remission. Complete remission (CR) included variants with recovery and partial recovery of hemopoiesis. In several patients, complete remission was registered in bone marrow, but extramedullary lesions were found in them.

Statistical evaluation

Descriptive statistics were used for the patients' characteristics and response to treatment using. Differences in response to treatment were evaluated with chi-square test. The variables with a significance levels of <=0.1 in the univariate analysis were selected for evaluation with logistic regression. The analyses were performed in SPSS ver. 17.0.

Results

The entire group of patients consisted of 182 children and adults at the age of 1 to 72 years old, including 78 children and adolescents up to 18 years, and 104 adults. 128 patients were treated with blinatumomab, 54 patients received inotuzumab ozogamicin. Baseline characteristics of the patients are shown in Table 1. The patients were classified by their mutational status at the time of onset of the disease, i.e., 161 (88%) cases of Ph-negative B-ALL and 21 (12%) patients with Ph-positive B-ALL. The mixed-lineage leukemia (MLL1) gene was detected in 17 (9%) patients: 9 with infant ALL, 2 in children over 1 year at the time of onset of disease and 6 in adults. Depending on occurrence of past relapses, the patients were divided into those who developed relapses after previous allo-HSCT 46 (25%) cases, or after chemotherapy (n=127, 70%) and primary resistance cases (n=9, i.e., 5%). Before blinatumomab treatment, 69 (54%) patients had molecular relapses, i.e., minimal residual disease (MRD), and 59 (46%) patients from this group. All the patients (n=54) who received inotuzumab had hematological relapses. Time of observation was from 23 to 730 days (median 244 days). In our study, most patients received 1-2 courses of blinatumomab and most patients received one cycle of inotuzumab ozogomicin. Patients with r/r Ph-positive B-ALL received different tyrosine kinase inhibitors (dasatinib 13, imatinib 6, nilotinib 2).

Clinical response in the whole group patients who received blinatumomab or inotuzumab was high both in adult and children groups, 83% and 69%, respectively, and most

Table 1. Clinical characteristics of B-ALL patients included into the study

Clinical/demographic feature (n=182)	Treatment with anti-CD19 (blinatumomab), n=128 (70% of total)	Treatment with anti-CD22, (inotuzumab) n=54 (30% of total)
Sex		
Male	74 (58)	30 (55)
Female	54 (42)	24 (44)
Age group, years		
0-18	52 (40)	26 (48)
>18	76 (60)	28 (52)
Cytogenetics/molecular genetics		
t(9;22)BSR-ABL+	18 (14)	3 (6)
t(4;11)MLL+	14 (10)	3 (6)
Relapse	123 (96)	50 (93)
Patients with refractory the previous CT	5 (4)	4 (7)
Molecular relapses history:		
Patients in first CR	28 (40)	0
Patients in second CR	33 (48)	0
Patients in third and >CR	8 (12)	0
Status before therapy		
CR with MRD+	69 (54)	0
HR	59 (46)	54 (100)
After treatment of blinatumomab	–	22 (44)

patients achieved complete remission (CR). In blinatumomab group, CR was registered in 57 adult patients (76%) and in 28 patients (52%) under 18 y.o. In inotuzumab group, overall response rate in adults was 82%, in children and adolescents, 81%; CR was achieved in 14 adult patients (50%), and in 14 children (58%) as seen from Fig. 1, A. The patients with cytogenetic or molecular genetics prognostic factors had high responses as well. Ph+ B-ALL in blinatumomab group had overall response in 84%, including 67% with CR. All Ph+ B-ALL patients in the inotuzumab group had hematological remission. The patients with MLL translocation had worst overall response compared to patients without MLL translocation, i.e., 41% and 65% of general group, respectively (Fig. 1, D). Overall responses in patients with relapses after previous HSCT and relapses after CT were comparable, 28 (63%) and 85 cases (63%) (Fig. 1, B). The patients who had molecular relapses before therapy with blinatumomab had higher response than patients with hematological relapses (90% *vs* 58%), as shown in Fig. 1, C. Multivariate analysis in our study showed that only age (p=0.001) and disease status (p=0.01) before blinatumomab or inotuzumab therapy showed statistical significance (Table 2). Previous exposition on blinatumab did not influence the response to inotuzumab ozogamicin, i.e., 89% *vs* 81% of responding patients (p=0.46) in blinatumomab-naïve *versus* blinatumomab-exposed cases.

Discussion

We have assessed high efficacy of blinatumomab and inotuzumab ozogamicin in a heterogeneous cohort of r/r B-cell ALL of children and adults in real clinical practice. After these therapies, high rate of complete remission (CR) was observed in all subgroups, including patients with cytogenetics/ molecular genetic prognostic factors, e.g., in the cases with Ph-positive r/r B-ALL. If comparing our study with recent work that used combination of TKI and blinatumomab in patients with Ph-positive r/r B-ALL [19], our results seem to be something better. In our study, CR was achieved in 57% *versus* 36%, probably, due to high proportion of patients treated for MRD unlike in the previous study where majority of patients had hematological relapse. Patients with r/r B-ALL and MLL translocation achieved CR in 41% cases. These data demonstrate an opportunity of using this treatment in patients from high-risk group, but further studies are required to demonstrate whether the response rate is significantly lower than in general cohort.

Overall response in pediatric subgroup in our study differed significantly from adult patients because of probable differences in biology, e.g., genomic profiling in pediatric B-ALL more often reveals mutations in NRAS, KRAS genes, and MLL rearrangement. ETV6/RUNX1 (E/R) was the most common fusion gene in pediatric B-ALL as well [20]. Differences in immune system may also play a role in response rates [21] The observation that blinatumomab works better in MRD setting than in hematological remission confirms the previous report on clinical trials of Germany group, where 80% of molecular CR was documented [22]. Inotuzumab ozogamicin is effective, regardless the tumor burden: the overall response was 81%. The response rate was comparable to results of adult and pediatric registration study [11, 12, 13, 14]. Monoclonal antibodies present such opportunity, providing reliable approach to achieve CR in r/r B-ALL patients before sequential HSCT.

Conclusion

1. Both blinatumomab and inotuzumab ozogomicin are effective in patients with r/r B-ALL.

2. Blinatumomab is more effective in patients with molecular relapses.

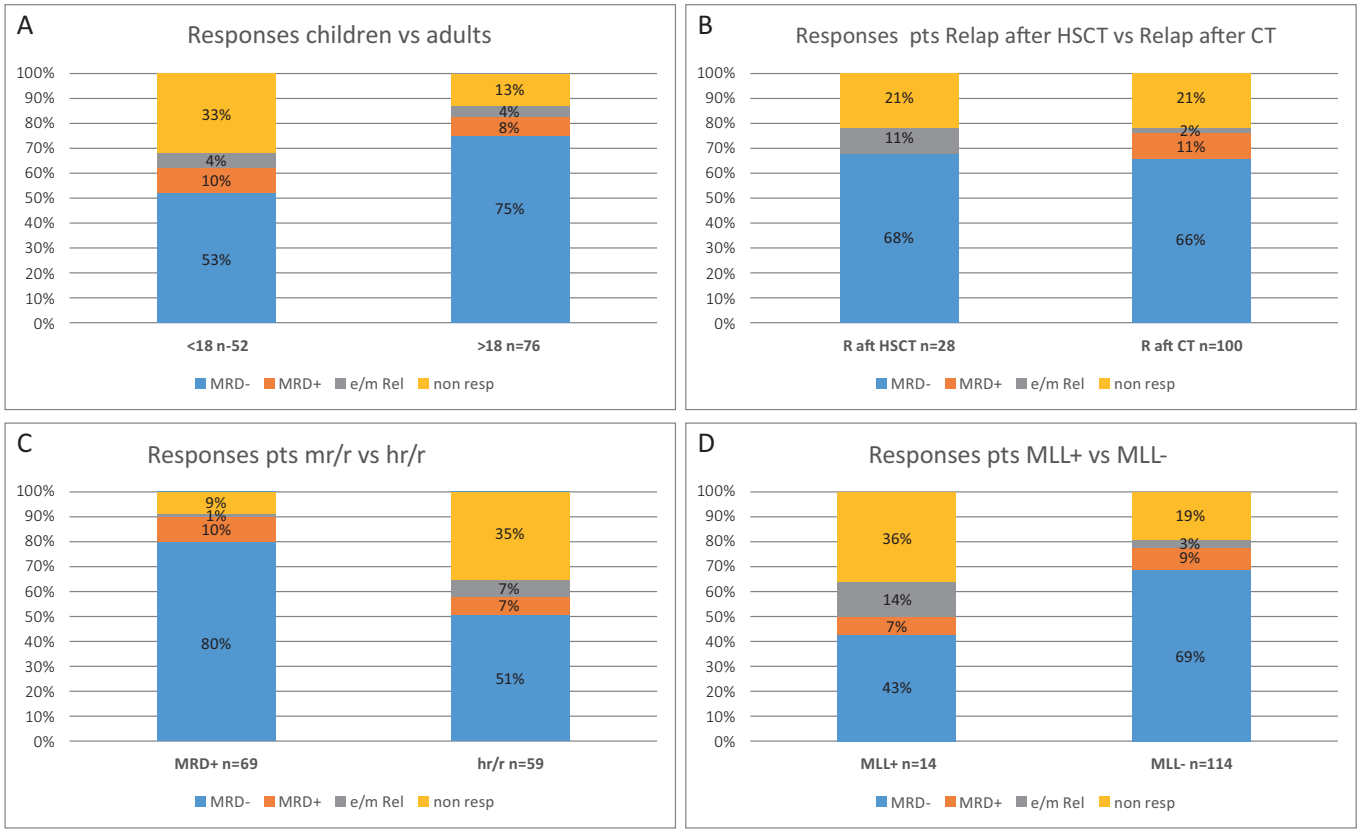

Figure 1. Types of responses to antibody-based drug treatment in r/r B-ALL patients. A, Children *vs* adults; B, Patients with relapses following previous HSCT *vs* preceding CT; C, Patients with molecular relapses *vs* hematological relapses; D, Cases with MLL translocation *vs* patients without MLL translocation. The patients were classified by different types of minimal residual disease (bottom line of the pictures)

Table 2. Multivariate analysis of some factors predictive for treatment response

Characteristics	p	Exp(B)	95% CI for Exp(B)	
			Lower	Upper
Age	0.001	3.819	1.744	8.223
Cytogenetics/molecular genetics prognostic factors (Ph+, MLL+)	0.9	0.971	0.609	1.548
Previous therapy (CT, HCST)	0.1	0.188	0.746	4.455
Status before blinatumomab or inatuzumab	0.01	0.018	0.153	0.841

3. Blinatumomab-refractory patients can be salvaged with inotuzumab ozogamicin.

4. Results in real-life clinical practice are comparable to extensive registration studies.

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Особенности ответа на терапию блинатумомабом и инотузумабом озогамицином у больных с рецидивирующим/рефрактерным В-клеточным острым лимфобластным лейкозом в реальной клинической практике

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Резюме

Аллогенная трансплантация гемопоэтических стволовых клеток остается наиболее эффективным методом излечения пациентов с рефрактерным течением/рецидивами В-клеточного острого лимфобластного лейкоза (р/р В-ОЛЛ). Полная ремиссия заболевания без признаков минимальной остаточной болезни является ключевым фактором успешного исхода. Моноклональные антитела (биспецифические и коньюгаты) представляют собой эффективные опции в достижении ремиссии у этих пациентов. Нашей целью было обобщение результатов одноцентрового нерандомизированного исследовапния для изучения результатов терапии блинатумамобом и инотузумаб-озогамицином у детей и взрослых в гетерогенной когорте больных р/р В-ОЛЛ. Результаты одноцентрового, нерандомизированного пилотного исследования в реальной клинической практике продемонстрировали высокий уровень ответа на данный вид терапии в гетерогенной когорте пациентов с р/р В-ОЛЛ. Исследуемая группа включала 182 пациента р/р В-ОЛЛ, возраст от одного года до 72 лет, 128 пациентов получали блинатумомаб, 54 пациента получали инотузумаб озогамицин. Уровень общего ответа был высоким в обеих группах – 96 (75%) и 44 случая (82%), соответственно. Главными предикторами ответа были взрослый возраст (OR=3,819, 95% CI=1,744-8,223, p=0,001) и показания к терапии – гематологический рецидив или персистенция минимальной остаточной болезни (OR=0,018, 95% CI=0,153-0,841, p=0,01). Другие клинические или патологические параметры не оказывали существенного влияния на ответы на терапию.

Ключевые слова

В-клеточный острый лимфобластный лейкоз, рефрактерный и рецидивирующий, моноклональные антитела, блинатумомаб, инотузумаб озогамицин, общий ответ.