BRIEF REPORT
DOI: 10.4274/tjh.galenos.2025.2025.0356

Salvage Treatment Options for Post-Transplant Relapse in Children with Early/Very Early Relapse of Acute Lymphoblastic Leukemia: A Single Center Experience

Akut Lenfoblastik Lösemili Erken/Çok Erken Relaps Olan Çocuklarda Nakil Sonrası Relaps İçin Kurtarma Tedavisi Seçenekleri: Tek Merkez Deneyimi

Zühre Kaya, Serap Kirkiz Kayalı, Ahmet Bayramlı, Emine Yılmaz Orulluoğlu, Ülker Koçak
Gazi University Faculty of Medicine, Department of Pediatric Hematology, Ankara, Türkiye

Prof. Zühre Kaya, M.D., Gazi University Faculty of Medicine, Department of Pediatric Hematology, Ankara, Türkiye
zuhrekaya@gazi.edu.tr

August 23, 2025
November 10, 2025

Abstract
This study aimed to evaluate salvage treatment options for posttransplant relapse in children with early/very early relapse acute lymphoblastic leukemia (ALL). Forty consecutive high-risk ALL children were divided into two groups based on their salvage treatment for posttransplant relapse: Group 1 (n = 9) received purine nucleoside analogs [fludarabine/clofarabine-based regimens], while Group 2 (n = 8) received targeted agents [Blinatumomab, Bortezomib, and CART]. In Group 1, seven children received a fludarabine-based regimen, and two received a clofarabine-based regimen. In Group 2, five children received Bortezomib-based regimens, two received Blinatumomab, and one received CART. Group 2 showed a significantly higher cumulative survival rate (75% *vs* 22%) and lower grade 3 and 4 toxicity rates (13% *vs* 66%) compared to Group 1 (p<0.05). Based on our limited data, targeted agents may represent an effective treatment option and can be directly recommended for posttransplant relapse in high-risk children with ALL.
Key Words: Posttransplant relapse, children, targeted agents

Özet
Bu çalışmanın amacı, erken/çok erken relapsı olan akut lenfoblastik lösemili (ALL) çocuklarda nakil sonrası nüks için kurtarma tedavisi seçeneklerini değerlendirmektir. Kırk ardışık yüksek riskli ALL hastası, nakil sonrası relaps için kurtarma tedavisine göre iki gruba ayrıldı: Grup 1 (n = 9) purin nükleozid analogları [fludarabin/klofarabin bazlı rejimler] alırken, Grup 2 (n = 8) hedefe yönelik ajanlar [Blinatumomab, Bortezomib ve CART] aldı. Grup 1'de yedi çocuğa fludarabin, iki çocuğa ise klofarabin bazlı tedavi rejimleri uygulandı. Grup 2'de beş çocuğa Bortezomib bazlı tedavi rejimi, iki çocuğa Blinatumomab ve bir çocuğa CART uygulandı. Grup 2, Grup 1'e kıyasla anlamlı derecede daha yüksek kümülatif sağkalım oranı (%75'e karşı %22) ve daha düşük evre 3 ve 4 toksisite oranları (%13'e karşı %66) gösterdi (p<0,05). Sınırlı verilerimize dayanarak, hedefe yönelik ajanlar yüksek riskli ALL'li çocuklarda etkili bir tedavi seçeneği olabilir ve nakil sonrası nüks için doğrudan önerilebilir.
Anahtar kelimeler: Posttransplant relaps, çocuklar, hedef ajanlar

Introduction
In children with high-risk acute lymphoblastic leukemia (ALL), relapse after allogeneic stem cell transplantation (allo-SCT) can cause morbidity and mortality. There is no consensus on managing posttransplant relapse in these patients [1-3]. Purine nucleoside analogs, such as fludarabine and clofarabine-based regimens, have been used for years to treat pre- and posttransplant recurrence; however, maintaining complete remission (CR) is particularly challenging, especially in ALL patients with early/very early relapse, even after allo-SCT [4-8].

Nonetheless, recently developed targeted therapies have been successfully used to achieve CR in relapsed/refractory children with ALL [9-14].
We investigated the role of salvage therapies for posttransplant relapse in children with early/very early relapsed ALL.

Materials and Methods

This single-center retrospective study included 40 consecutive children with early/very early relapsed ALL undergoing allo-SCT between 2005 and 2024. Patients with late or isolated extramedullary relapse and refractory disease before SCT were excluded. The institutional ethics committee approved this study. The BFM protocols defined risk groups based on age, blast counts in peripheral blood on day 8 and marrow on days 15 and 33, flow-MRD on day 15 (since 2016), and cytogenetic markers (t(9;22) and t(4;11) [15,16].

Pretransplant relapse management

Our institutional approach was to commence the ALL-Rez-BFM-02 protocol as the first-line therapy for all relapsed patients. Treatment responses were assessed as described previously [4, 17, 18]. If these patients did not respond to the Rez-BFM-02 protocol before allo-SCT, they received second-line therapy in the form of purine nucleoside analogs [FLAG-IDA (Fludarabine, cytarabine, with/without idarubicin) or CLOVE (clofarabine, cyclophosphamide, and etoposide)] [4-7]. When these therapies achieved CR, all relapsed patients underwent allo-SCT.

Posttransplant relapse management

Patients were divided into two groups based on their salvage therapy for posttransplant relapse. Group 1 (n=9) included patients with second-line fludarabine/clofarabine-based regimens who had previously received Rez-BFM-02, while Group 2 (n=8) included patients with third-line targeted agents who had previously received at least two lines of therapy, such as fludarabine/clofarabine-based regimens and Rez-BFM-02, but had not responded. In Group 2, third lines of newer targeted agents, such as Blinatumomab, Chimeric antigen receptor T cells (CART), and a Bortezomib-based regimen with off-label use, were used to achieve CR [9-14]. After CR, the selected patients underwent a second allo-SCT. All drug toxicities were classified at http://evs.nci.nih.gov/ftp1/CTCAE/. The SPSS 26.0 program was used for analysis.

Results

Our transplant team performed 45 allo-HSCTs in 40 patients with early/very early relapsed ALL. There were no significant differences in demographic data between the two groups, except for toxicity and survival status (p>0.05) (Table 1).

Pretransplant and Posttransplant Remission Status

Using the Rez-BFM-02, pretransplant CR was obtained in 29 (72%) of very early/early relapse patients. The remaining 11 (28%) unresponsive patients were entered into CR with salvage therapies, including FLAG-IDA (73%) (n=8) and CLOVE (27%) (n=3) (Figure 1).

Posttransplant relapse occurred in 17 (42.5%) of 40 patients, including 9 (53%) in Group 1 and 8 (47%) in Group 2. In group 1, nine patients received fludarabine/clofarabine-based regimens in the posttransplant period. Four of them did not enter CR, and the other three patients refused any other therapies; all seven patients died. The remaining two patients achieved CR with FLAG and survived; only one received a second allo-SCT.

In Group 2, eight patients received targeted agents. Of them, two patients in very early relapse who received two cycles of blinatumomab underwent a second transplant. Since the other five patients in early relapse were not eligible for a second transplant, they received Bortezomib with off-label use. Only four had lived in CR for a median of 2 years (1.0-3.5 years). The remaining only one patient died of leukemia progression. A 13-year-old child was diagnosed with ALL at our center, but he later developed a combined BM and central nervous system (CNS) recurrence. He achieved CR with FLAG-IDA at our center and then moved to Germany. His mother informed us that he underwent allo-SCT followed by CART in Germany. Although he was leukemia-free for a long time, he died of an isolated CNS relapse after 11 years of CART (Figure 1).

Toxicity and Survival

Group-1 (67%) had a significantly higher risk of posttransplant grade 3 and 4 toxicity compared to Group-2 (13%) (p<0.05). Grade 3 and 4 mucositis, diarrhea, and myelosuppression were found in six patients in Group 1, and only one patient in Group 2. Grade 1 and 2 mucositis, diarrhea, myelosuppression, mild hepatotoxicity, and neurotoxicity were observed in three patients in Group 1 and seven patients in Group 2. Only one patient in Group 2 developed cytokine release syndrome. The cumulative survival rate was significantly lower in Group 1 (22%) than in Group 2 (75%) ($p < 0.05$) (Figure 2).

Discussion

Treatment for posttransplant relapses in pediatric ALL has yet to be definitively established. In a study, 203 patients with recurrent ALL achieved an 85% CR after following the several Rez-BFM 87/95/96/02 protocols [19]. Similarly, Rez-BFM-02 resulted in CR for 72% of our patients with very early relapse/early relapse before allo-SCT. Various salvage regimens are recommended for relapsed ALL patients [4-14]. In a few studies, the rate of CR with fludarabine-based regimens was between 42% and 69% in relapsed/refractory children with acute leukemia [4,5]. Although experience with clofarabine after allo-SCT was limited, a meta-analysis revealed that a clofarabine-based regimen resulted in a 16% rate of CR in relapsed children with ALL [6,7]. Similarly, two-thirds of our patients receiving fludarabine-based chemotherapy and one-third of those receiving clofarabine-based regimens achieved CR. Furthermore, these patients reported increased toxicity and a higher

mortality rate, which was consistent with our results. In recent years, new drugs such as bortezomib, blinatumomab, and CART have contributed to CR if there was no response to at least two lines of therapy following allo-SCT [9-14]. In a few studies, a proteasome inhibitor called bortezomib-based regimen resulted in a CR rate of 63-72% in patients with recurrent ALL before allo-SCT [10, 11]. However, we used bortezomib off-label in patients with recurrent ALL following allo-SCT and achieved similar CR in 80% of cases. Despite our limited experience with bortezomib, we believe it may be a promising targeted therapy for posttransplant recurrent ALL.

Blinatumomab is a bispecific T cell engager that targets both CD19 on leukemic cells and CD3 on cytotoxic T cells, destroying leukemic blasts. It is commonly used in children with relapsed/refractory ALL before allo-SCT [12]. In a systematic review, blinatumomab may serve as a good alternative for achieving CR in adults with posttransplant relapse; however, phase 1/2 trials using blinatumomab for posttransplant relapse are still ongoing in children [13]. Our limited experience with two children suggests that administering at least two cycles of blinatumomab before a second transplant could result in CR. Additionally, CART cells targeting CD19 after SCT in patients with B-ALL were found to be safe and effective in a study [14]. Only one patient in our series received CART therapy for combined BM and CNS relapses after SCT, and he experienced an isolated CNS recurrence after 11 years. CART may be ineffective in sanctuary sites, including the CNS, as seen in our case. Our findings indicate that targeted agents are a promising therapy option for posttransplant relapse in high-risk ALL children and can be recommended directly; however, more research in a multicenter, homogeneous, larger population is required.

Statements and Declarations

Funding: The authors did not receive support from any organization for the submitted work.

Conflicts of interest/Competing interests: All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript. All authors read and approved the final manuscript.

Informed consent was obtained from parents

References

1. Elgazar S, Constantinou C. Paediatric Acute Lymphoblastic Leukaemia: A Narrative Review of Current Knowledge and Advancements. *Curr Oncol Rep.* 2024;26(12):1586-1599.

2. Hunger SP, Raetz EA. How I treat relapsed acute lymphoblastic leukemia in the pediatric population. *Blood.* 2020 Oct 15;136(16):1803-1812.

3. Sidhu J, Gogoi MP, Krishnan S, Saha V. Relapsed Acute Lymphoblastic Leukemia. *Indian J Pediatr.* 2024 Feb;91(2):158-167.

4. Yılmaz Bengoa Ş, Ataseven E, Kızmazoğlu D, Demir Yenigürbüz F, Erdem M, Ören H. FLAG Regimen with or without Idarubicin in Children with Relapsed/Refractory Acute Leukemia: Experience from a Turkish Pediatric Hematology Center. *Turk J Haematol*. 2017 Mar 1;34(1):46-51

5. Aygüneş U, Karagün BŞ, Şaşmaz I, Antmen AB. The outcome of relapsed childhood acute lymphoblastic leukemia after allogeneic hematopoietic stem-cell transplantations: A single-center experience. *Clin Transplant*. 2024;38(5):e15366.

6. Jeha S, Goto H, Baruchel A, Boëlle-Le Corfec E, Geffriaud-Ricouard C, Pieters R, Shin HY. Patient-Level Meta-analysis of Clofarabine in Acute Lymphoblastic Leukemia. *Adv Ther.* 2023 Dec;40(12):5447-5463.

7. Willasch AM, Salzmann-Manrique E, Krenn T, et al. Treatment of relapse after allogeneic stem cell transplantation in children and adolescents with ALL: the Frankfurt experience. *Bone Marrow Transplant*. 2017;52(2):201-208.

8. Parker WB. Enzymology of purine and pyrimidine antimetabolites used in the treatment of cancer. *Chem Rev*. 2009;109(7):2880-2893.

9. Goto H. Childhood relapsed acute lymphoblastic leukemia: Biology and recent treatment progress. *Pediatr Int*. 2015;57(6):1059-1066.

10. Bertaina A, Vinti L, Strocchio L, Gaspari S, Caruso R, Algeri M, Coletti V, Gurnari C, Romano M, Cefalo MG, Girardi K, Trevisan V, Bertaina V, Merli P, Locatelli F. The combination of bortezomib with chemotherapy to treat relapsed/refractory acute lymphoblastic leukemia of childhood. *Br J Haematol.* 2017 Feb;176(4):629-636.

11. Horton TM, Whitlock JA, Lu X, O'Brien MM, Borowitz MJ, Devidas M, Raetz EA, Brown PA, Carroll WL, Hunger SP. Bortezomib reinduction chemotherapy in high-risk ALL in first relapse: a report from the Children's Oncology Group. *Br J Haematol.* 2019 Jul;186(2):274-285.

12. Llaurador G, Shaver K, Wu M, Wang T, Gillispie A, Doherty E, Craddock J, Read J, Yassine K, Morales E, George A, Steffin D, Krance R, Martinez C, Heslop H, Salem B. Blinatumomab Therapy Is Associated with

Favorable Outcomes after Allogeneic Hematopoietic Cell Transplantation in Pediatric Patients with B Cell Acute Lymphoblastic Leukemia. *Transplant Cell Ther.* 2024 Feb;30(2):217-227.

13. Guo HP, Liu Y, Kang L, Liu C, Qin WW. Efficacy and safety of blinatumomab for the treatment of patients relapsing after allogeneic hematopoietic cell transplantation: a systematic review and meta-analysis. *Hematology.* 2024 Dec;29(1):2422151

14. Zhao YL, Liu DY, Sun RJ, Zhang JP, Zhou JR, Wei ZJ, Xiong M, Cao XY, Lu Y, Yang JF, Zhang X, Lu DP, Lu P. Integrating CAR T-Cell Therapy and Transplantation: Comparisons of Safety and Long-Term Efficacy of Allogeneic Hematopoietic Stem Cell Transplantation After CAR T-Cell or Chemotherapy-Based Complete Remission in B-Cell Acute Lymphoblastic Leukemia. *Front Immunol.* 2021 May 7;12:605766.

15. Kocak U, Gursel T, Kaya Z, Aral YZ, Albayrak M, Keskin EY, Belen B, Isık M, Oner N. ALL-BFM 95 treatment in Turkish children with acute lymphoblastic leukemia--experience of a single center. *Pediatr Hematol Oncol.* 2012 Mar;29(2):130-40.

16. Baytan B, Evim MS, Güler S, Güneş AM, Okan M. Acute Central Nervous System Complications in Pediatric Acute Lymphoblastic Leukemia. *Pediatr Neurol.* 2015 Oct;53(4):312-8.

17. Argyriadi EA, Steffen IG, Chen-Santel C, et al. Prognostic relevance of treatment deviations in children with relapsed acute lymphoblastic leukemia who were treated in the ALL-REZ BFM 2002 study. *Leukemia*. 2025;39(2):337-345.

18. Tüfekçi Ö, Evim MS, Güneş AM, Celkan T, Karapinar DY, Kaya Z, Baysal B, Baytan B, Koçak Ü, Yilmaz Ş, Çinar S, Ören H. Assessment of Minimal Residual Disease in Childhood Acute Lymphoblastic Leukemia: A Multicenter Study From Turkey. *J Pediatr Hematol Oncol.* 2022 Mar 1;44(2):e396-e402.

19. Reismüller B, Attarbaschi A, Peters C, Dworzak MN, Pötschger U, Urban C, Fink FM, Meister B, Schmitt K, Dieckmann K, Henze G, Haas OA, Gadner H, Mann G; Austrian Berlin-Frankfurt-Münster (BFM) Study Group. Long-term outcome of initially homogenously treated and relapsed childhood acute lymphoblastic leukemia in Austria--a population-based report of the Austrian Berlin-Frankfurt-Münster (BFM) Study Group. *Br J Haematol.* 2009 Feb;144(4):559-70.

Legends to Figures and Tables

Table 1. Demographic, Clinical, and Laboratory Features of the 17 Patients with Posttransplant-Relapsed ALL

Table 1. Demographic, Clinical, and Laboratory Features of the 17 Patients with Posttransplant-Relapsed ALL

Variables	Fludarabine-Clofarabine-based regimens in Group 1 *n*=9	Targeted agents in Group 2 *n*=8	*p*
Gender, *n (%)*			
Male	8(88%)	6(75%)	0.45
Female	1(12%)	2(25%)	
Age(years)	6.9±2.8	5.4±3.5	0.66
Leukemia Types, *n (%)*			
T-ALL	1(12%)	0(0%)	0.93
B-ALL	8(88%)	8(100%)	
Risk Groups			
High-risk	2(22%)	5(62%)	0.19
Medium-risk	4(45%)	1(13%)	
Standard-risk	3(33%)	2(25%)	
Relapse types, *n (%)*			
Very early	5(55%)	4(50%)	0.60
Early	4(45%)	4(50%)	
Transplant characteristics			
Donor types, *n (%)*			
Related donor	7(78%)	6(75%)	0.66
Unrelated donor	2(22%)	2(25%)	
Conditioning, *n (%)*			
TBI	5(55%)	5(62%)	0.58
non-TBI	4(45%)	3(38%)	
Product types, *n (%)*			
BM	3(33%)	4(50%)	0.42
PB	6(67%)	4(50%)	
Acute GVHD, *n (%)*			
Yes	5(55%)	4(50%)	0.60
No	4(45%)	4(50%)	
Posttransplant characteristics			
Relapse site,*n (%)*			
Isolated BM	6(67%)	6(75%)	0.56
Combined BM*	3(33%)	2(25%)	
Time from transplant to relapse,*n (%)*			
Days			
≤100	4(45%)	2(25%)	0.37
>100	5(55%)	6(75%)	
Second allo-SCT, *n (%)*			
Yes	1(12%)	4(50%)	0.11
No	8(88%)	4(50%)	
Toxicity grading, *n (%)*			
Grade 1-2	3(33%)	7(87%)	0.03
Grade 3-4	6(67%)	1(13%)	
Survival status, *n (%)*			
Alive	2(22%)	6(75%)	0.04
Died	7(78%)	2(25%)	

ALL: Acute lymphoblastic leukemia; BM: Bone marrow; PB: Peripheral blood; TBI: Total body irradiation; GVHD: Graft versus host disease, Allo-SCT:Allogeneic stem cell transplantation,

*Combined BM: Central nervous system in 3 patients and testis in 2 patients

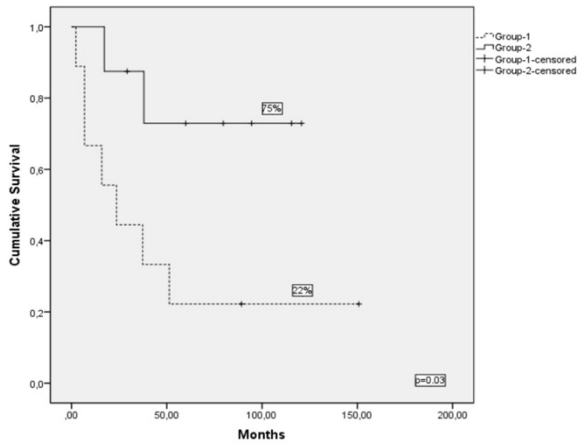

Figure 1. Flow chart demonstrating the outcome of 40 children with relapsed acute lymphoblastic leukemia

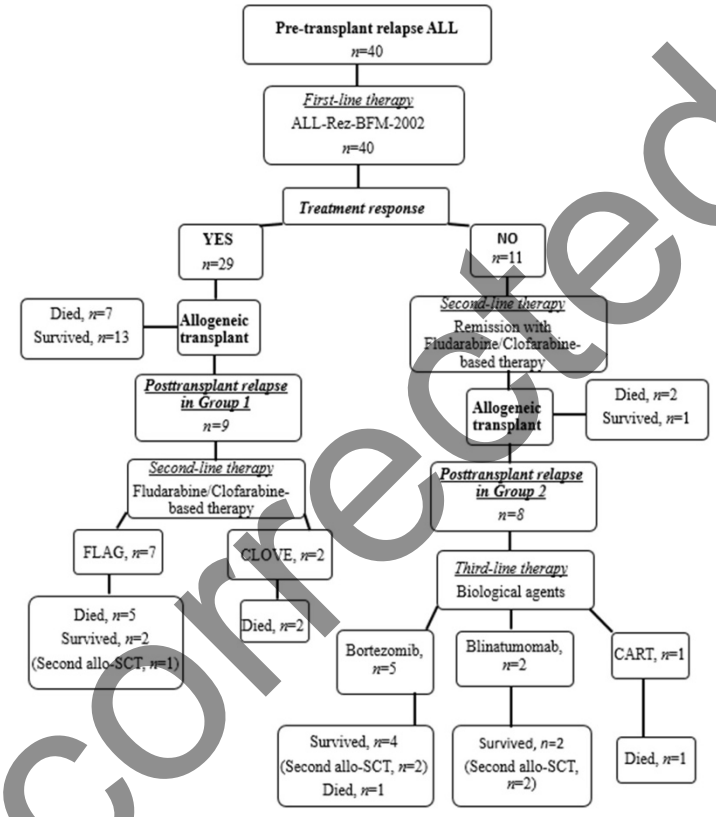

Figure 2. The Cumulative survival of children with relapsed acute lymphoblastic leukemia based on a fludarabine/clofarabine-based regimen in Group 1 and targeted agents in Group 2