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Allogeneic hematopoietic stem cell transplantation in children and adults with acute lymphoblastic leukemia*

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Summary

The aim of this study was to evaluate efficacy of allogeneic hematopoietic stem cell transplantation (allo-HSCT) in acute lymphoblastic leukemia (ALL), and to specify significant factors affecting clinical outcomes. Patients and methods. The study included 354 ALL patients aged 1 to 61 years who underwent allo-HSCT over a period of 1995 to 2015. Before HSCT, 24% of patients were in the 1st remission, 26% – in 2nd remission, 17%, in the ≥ 3rd remission; 34% of patients had active disease. Results. Overall survival (OS) was 47% when HSCT was performed in remission status versus 18% in patients transplanted in active disease state (p <.0001). Appropriate relapse incidence (RI) comprised 26% and 50%, respectively (P <.0001). Five-year OS was similar in children and adults (48% and 47% respectively, p>0.2). Pre-transplant remission state showed certain correlations with OS in pediatric and adult transplant patients, i.e., 79% vs 60% for HSCT in 1st remission; 40% vs 43% in 2nd remission, and 33% vs 23% for the patients treated in ≥ 3rd remission. ALL RI in children and adults were also comparable for HSCT carried out in 1st remission (21% vs 32%), 2nd remission (33% vs 17%), and 17% vs 23% for HSCT performed in ≥3rd remission (p>0.2). Most ALL patients underwent myeloablative conditioning regimen (MAC) before allo-HSCT (n=89). OS in MAC group was 53% versus 40% among patients who underwent reduced-intensity conditioning (RIC) regimens (n=70, p=0.04). The conditioning regimen intensity did not correlate with the RI after allo-HSCT (24% and 30% (MAC vs RIC respectively), p=0.09). Non-relapse mortality (NRM) did not significantly differ for children and adults (32% vs 37%, p>0.2), being dependent on the disease state: 21% vs 25% after HSCT in the 1st remission; 31% and 43%, when treated in the 2nd remission, and 50% vs 61% if transplanted in ≥3rd remission. Conclusion. Allo-HSCT from an HLA-matched related or unrelated donor is indicated in patients with high-risk ALL in first remission and in all the patients in the second remission.

Keywords

acute lymphoblastic leukemia, allogeneic bone marrow transplantation, conditioning regimens, survival rates

* The paper is based on a presentation at the EWALL meeting (Moscow, 26-27 June 2015)

Introduction

Acute lymphoblastic leukemia (ALL) represents from 25 to 30% of all malignancies in childhood, and less common (ca.1%) in adults. Modern programmed chemotherapy (CT) allows of achieving stable remission in up to 90% of children and 40% of adults. However, efficiency of chemotherapy in high-risk ALL patients is still inferior in the both age groups; five-year disease-free survival (DFS) does not exceed 40% and 25%, respectively [7, 11, 12].

Allogeneic hematopoietic transplantation (allo-HSCT) is an effective method of treatment for the high-risk ALL patients, both due to a cytostatic effect of conditioning regimen upon leukemic clonogenic cells, and immunoadoptive «graft-versus-leukemia» effect exerted by donor T cells [1, 14]. However, higher risk of a non-transplant-related mortality (NRM) limits wider application of this treatment modality. High probability of severe graft-versus-host disease (GvHD) is also possible, due to excessive alloreactivity of graft, thus often leading to death [19]. Generally, an increased therapeutic efficiency is observed, due to advent of novel targeted therapies, wider application of reduced-toxicity conditioning (RIC) regimens, and improved quality of supportive care. Therefore, current indications for allo-HSCT in pediatric and adult ALL are subject to permanent revisions [9]. The aim of our study was to evaluate clinical efficacy of allo-HSCT in ALL, and to identify significant factors which may affect general outcome in this clinical setting.

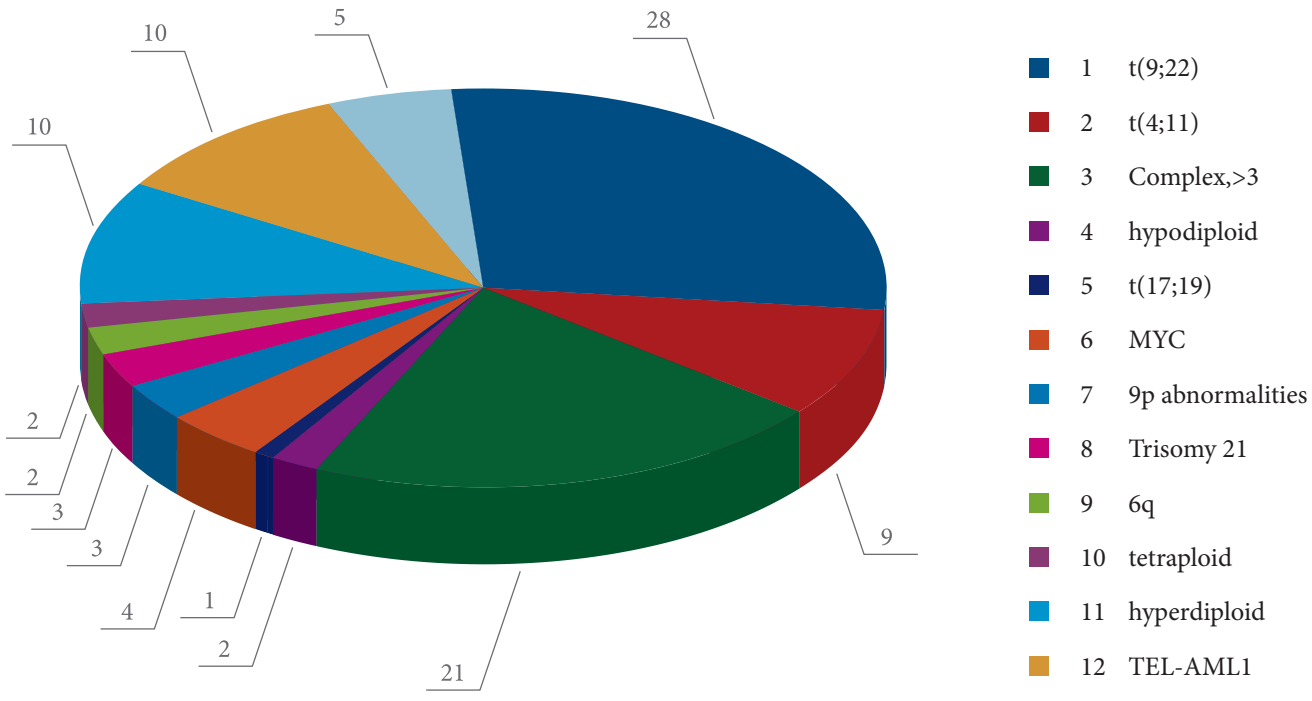
Patients and methods

The study included 354 patients with ALL (1 to 61 years old) who underwent allo-HSCTs from 1995 to 2015.

Age distribution of the patients was as follows: under 10 years, 72 (21%); 11-20 years, 131 (37%); 21-30 years, 100 (28%); 31-40 years, 29 (8%); over 40 years, 22 (6%). The median age was 22 years.

The patients were classified into distinct cohorts, according to EGIL phenotypic classification, as follows: B-ALL Philadelphia chromosome (Ph)-negative was identified in 54% of total case number including pro-B ALL (23%), common-B ALL (36%), pre-B ALL (17%), mature-B ALL (4%), B-lineage (20%). The patients with Ph (+) B-ALL made up 27% of total ALL cohort. In this group, we found pro-B ALL (11%), common-B ALL (70%), pre-B ALL (4%), and B-lin (15%). T-cell ALL was revealed in 19% of cases: pro-T (12%); pre-T (44%); cortic-T (9%), mature-T (3%) and T-lineage (32%).

Primary cytogenetic data were available for 74% of the patients, and initial molecular biology diagnostics was performed in 57% of the cases. Cytogenetic and molecular (RT-PCR) findings in the patients are shown in Fig. 1 and 2.



62% – unfavorable karyotype

Figure 1. Distribution of patients depending on cytogenetic abnormalities

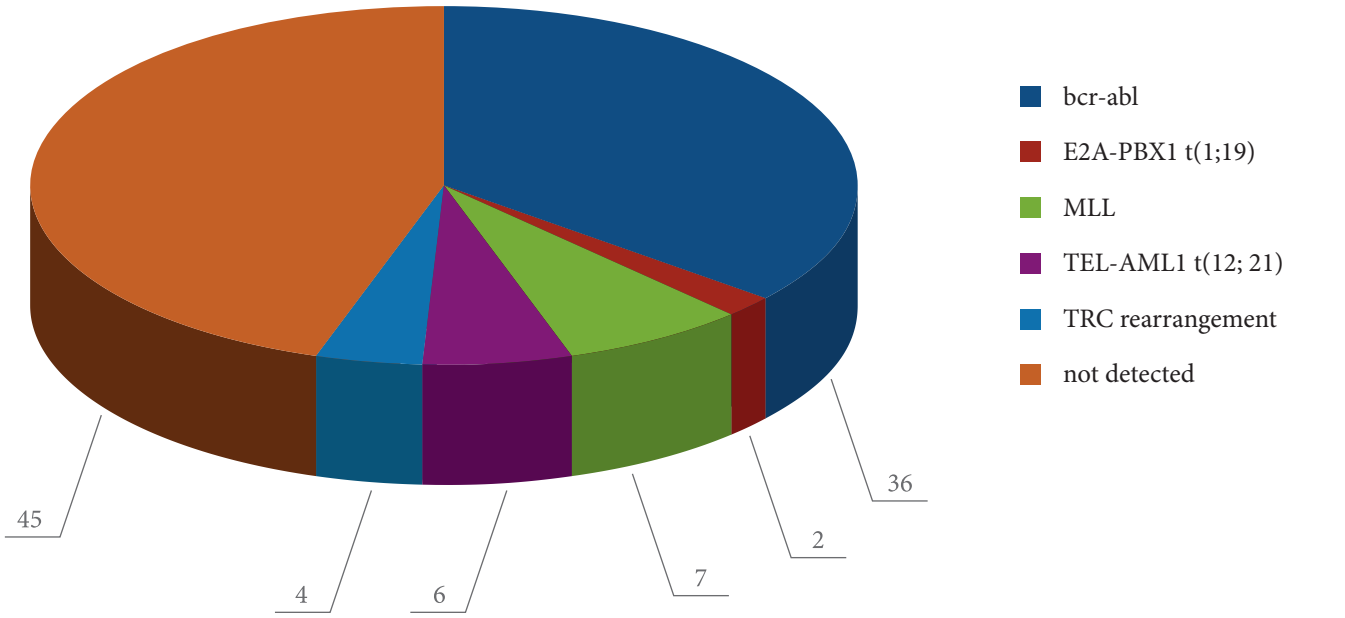


Figure 2. Distribution of patients depending on molecular abnormalities

Indications for allo-HSCT in the 1st remission were as follows: (1) high risk group (leukocytosis ≥ 30.0×10^9/L for B-ALL; ≥ 100.0×10^9/L for T-ALL, BI ALL and TI/TII / T IV EGIL phenotypes; (2) specific chromosome translocations, i.e., t(9; 22)(q34;q11), t(4; 11) (q21;q23), or t(8; 14)(q24.1;q32); complex karyotypic abnormalities (≥ 5), hypodiploid karyotype (<44 chromosomes), and/or absence of remission following induction therapy.

Myeloablative conditioning (MAC) included Busulfan 16 mg/kg and Cyclophosphamide 120 mg/kg. Reduced intensity conditioning (RIC) regimens contained a combination of Fludarabine (150 mg/m^2) and Busulfan (8mg/kg), or Melphalan (140 mg/m^2).

Acute and chronic GVHD prophylaxis included Cyclosporin A, or Tacrolimus combined with Methotrexate (15 mg/m^2 on D+1 and 10 mg/m^2 on the D+3 and D+6), or Mycophenolate Mofetil (30 mg/kg 2 times daily). GVHD prophylaxis for matched unrelated allo-HSCT was enhanced by antilymphocyte globulin (ATGAM) at a dose of 60 mg/kg. Since 2014, GVHD prophylaxis, especially in haploidentical HSCTs, included Cyclophosphamide (50 mg/kg on D + 3 and D + 4 post-transplant).

Conditioning regimens with reduced toxicity were administered to heavily pretreated patients with different complications associated with chemotherapy, subjects over 40 years old and pts with high comorbidity index. General characteristics of recipients, donors and graft properties are shown in Figure 3.

At the time of allo-HSCT, 24% of patients were in 1st remission, 26% – in 2nd remission, 17%, in ≥ 3rd remission, whereas 4% of the patients had active disease.

Statistical evaluation was performed with SPSS Statistics version 17. Overall survival (OS) was calculated with Kaplan-Meier method, whereas non-relapse mortality (NRM), and relapse incidence (RI) were assessed with R Statistic software. A log-rank test was used to compare OS, and exact Fisher test was applied for the share analysis. Distinct milestones were taken for evaluation, i.e., dates of birth, HSCT, early death and relapse. Initial terms of acute and chronic GVHD were also taken for clinical analysis. The survivors remaining in remission state by the end of data acquisition were censored by the 01/10/2015.

Results

Five-year OS of patients after allo-HSCT was 47% if transplanted in remission, as compared to 18% for the patients who underwent HSCT in active disease ($p < 0.0001$), relapse rates were 26% and 50% ($P < 0.0001$), respectively (Fig. 4).

Further analysis was performed for those patients who were in remission at the time of allo-HSCT (n=159). The type of ALL has no effect on overall and event-free survival. Five-year OS of children and adults was 48% and 47% ($p>0.2$).

The disease state pre-transplant exerted some influence upon the OS rates in children and adults, i.e., 79% *vs* 60% for allo-HSCT in 1st remission; 40% *vs* 43% in 2nd remission, and 33% *vs* 23% for the patients treated in ≥ 3rd remission (Fig. 5). The RI after allo-HSCT in children and adults were also comparable for patients transplanted in the 1st remission (21% *vs* 32%), 2nd remission (33% *vs* 17%), and 17% *vs* 23% for the patients transplanted in ≥3rd remission ($p>0.2$). Type of the donor and source of the graft did not affect OS. However, OS in cases of allo-HSCT from HLA-matched donor was higher than from HLA-mismatch donor (51% *vs* 25%, $p=0.002$), as seen from Fig. 6. Moreover, OS rate after allo-HSCT from matched related donors was 62%, from unrelated donors – 44%, from unrelated HLA-mismatched donors – 25% ($p>0.07$).

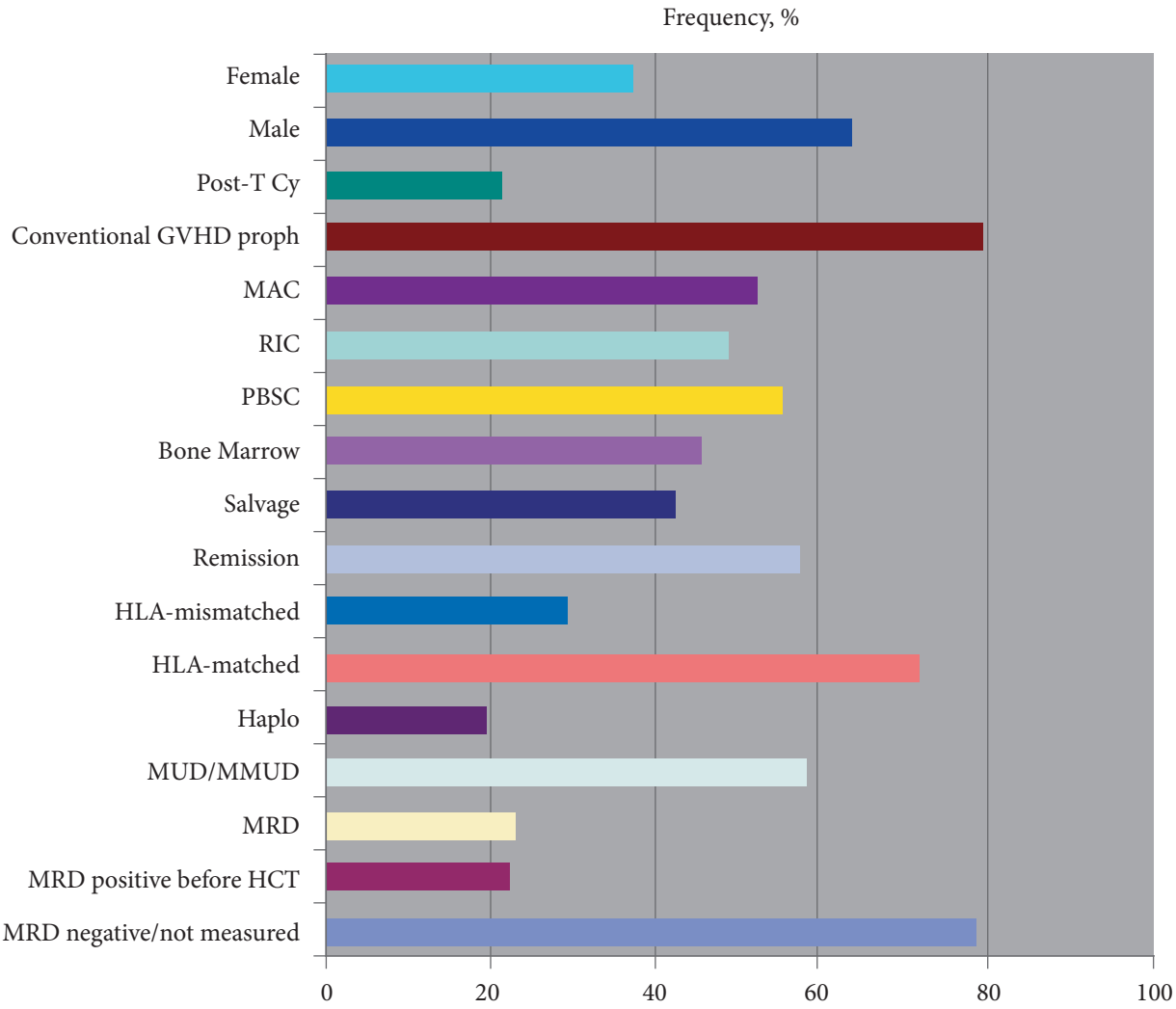


Figure 3. Characteristics of recipients, donors and transplant types

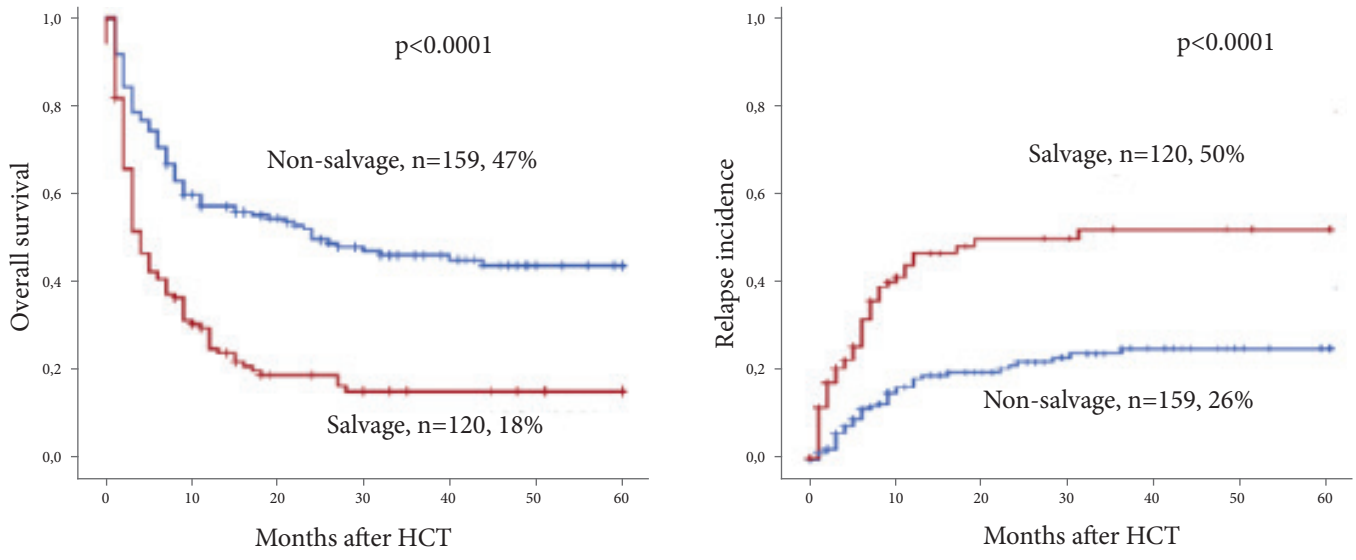


Figure 4. Overall survival and relapse incidence after allo-HSCT

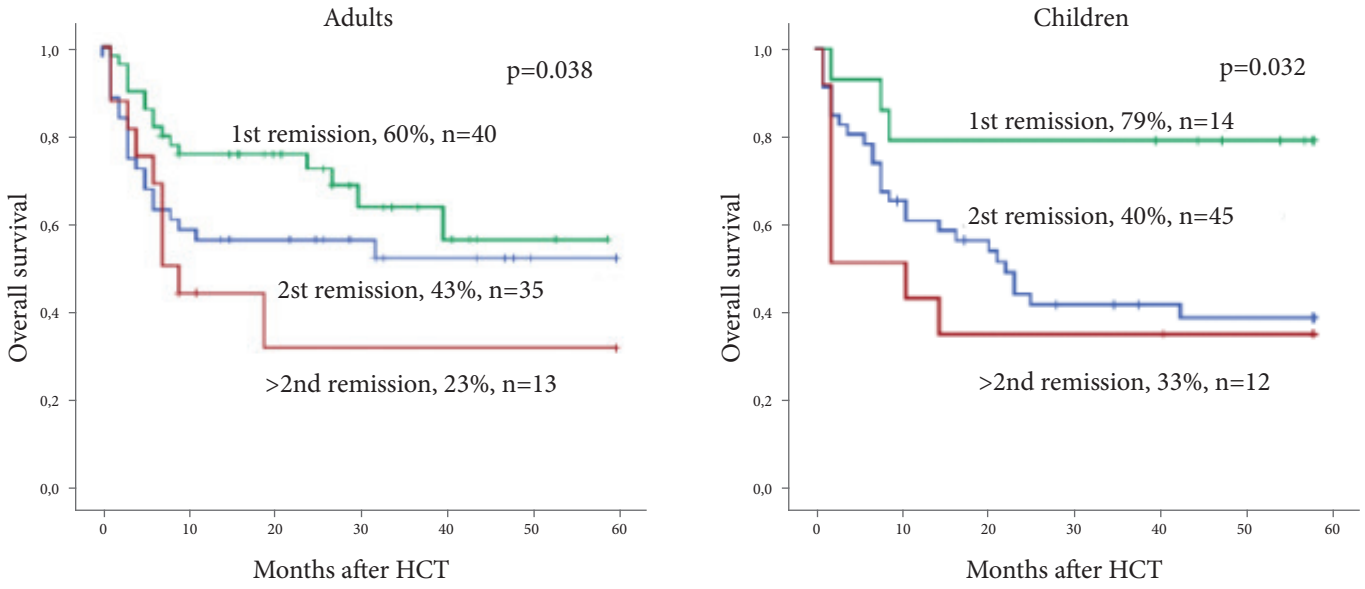


Figure 5. Overall survival in pediatric and adult ALL depending on the disease status at the time of allo-HSCT

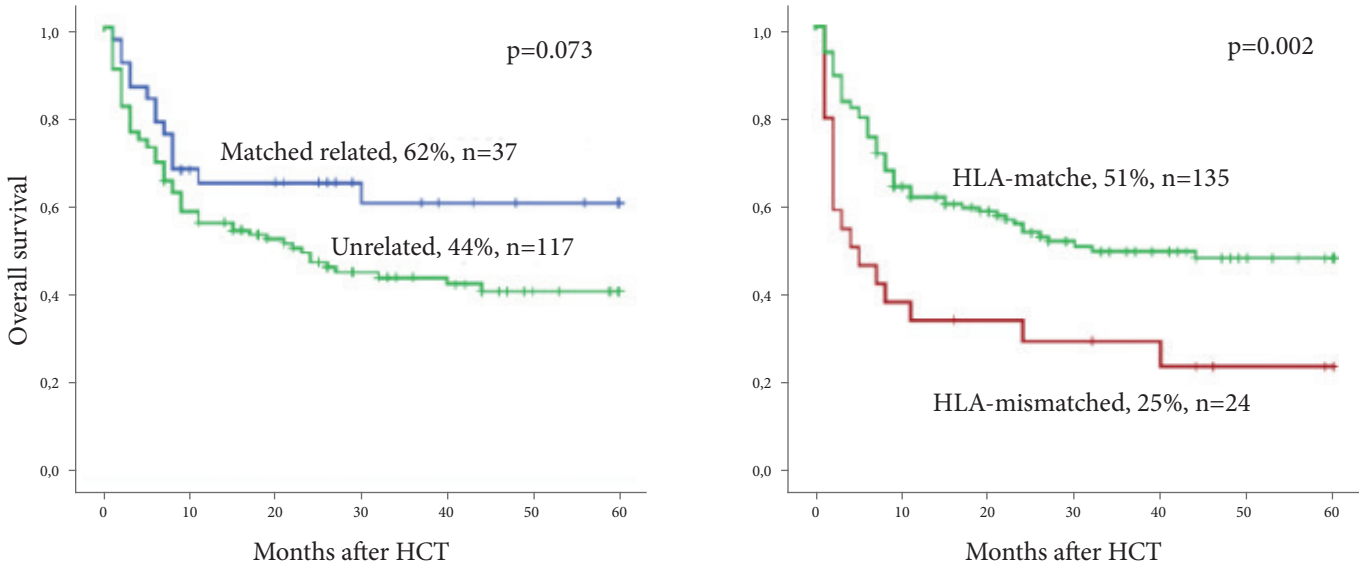


Figure 6. Overall survival after allo-HSCT depending on the donor type and HLA-compatibility of the donor and recipient

Most patients received MAC regimens (n= 89). OS in this group was 53% *vs* 40% in RIC group (n =70, p =0.04). Intensity of the conditioning regimen did not show statistically significant impact on the NRM (28% and 35%, p=0.06) and on the RI (24% and 30% respectively, p=0.09).

RI in children and adults were also comparable when treated in the 1st remission – 21% and 32%, when transplanted in the 2nd remission – 33% and 17%, if treated in the ≥3rd remission, 17% and 23% respectively, p>0.2. In our study the RI differed for distinct cytogenetic risk groups: in high risk group it was 36%, in the intermediate-risk group, 31%, p= 0.2 (Fig. 7). In most cases, a relapse occurred within 1st year after allo-HSCT (57%). In some patients with early ALL relapse, clonal evolution was detectable, i.e., emergence of new cytogenetic abnormalities (Table 1).

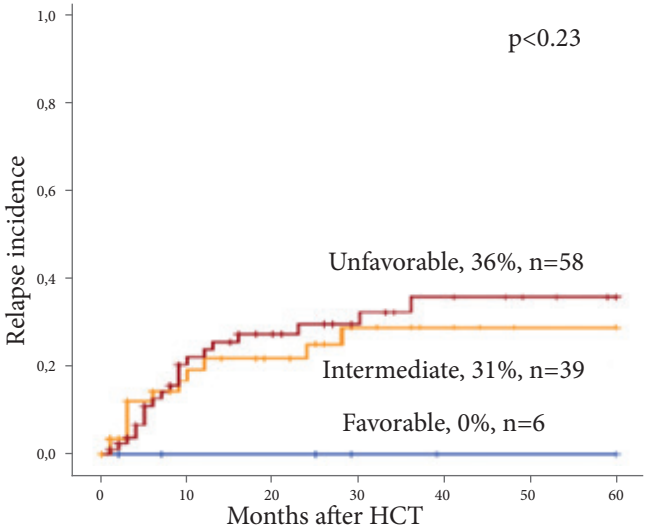


Figure 7. The influence of cytogenetic risk group at the relapse incidence

Table 1. Post-transplant evolution of leukemia clones in relapsed ALL

№	Before HCT	Relapse after HCT
1 m, 42	46,XY,t(9;22)(q34;q11) t(2;7)(p21;22), add(21)(q22) add(22)(p13)	idem, der(1)t(1;?)(q21;?), add(1)(q34), add(4)(p16), der(5)t(5;?)(q31;?)x2, add(7) (p22),del(11)(q23), add(14) (p11),
2 f, 37	47,XX, t(9;22)(q34, q11),+Ph	47,XX,der(6)t(6;12;13), del(13)(q13), -9, der(12) t(6;12), +der(22)t(9;22),+22
3 f, 30	46,XY,t(9;22) (q34;q11), del(12)(p12p13)	idem, i(8)(q10),add(11)(p13), add(15)(p11)
4 f, 13	48,XY,add(5) (q35),t(9;22) (q34;q11),+17,i(17) (q10),+19	49,XY,+X, del(2)(q33), +5, del(5)(q15q33),+8, t(9;22)(q34;q11), del(11) (p15),add(19)(q13)
5 m, 8	46,XX,t(4;11)(q21;q23)	46,XX,der(3)t(1;3) (q12;p25),t(4;11)(q21;q23),i(7) (q10)
6 f,10	50,XY,+X,+14,+21,+21	51,XY,+X,+8,+14,add(19) (p13),+21,+21
7 m,16	46,XX,t(4;11)(q21;q23)	47,XX,+X,+i(3)(q10),t(4;11) (q21;q23),del(16)(p13),- 17,add(21)(q22)

Immunoadoptive therapy (donor lymphocyte infusions) was carried out in 73 patients (20%) for prevention and/or treatment of relapses. Seventeen patients received DLI as monotherapy. For 56 patients, DLI was applied in combination with cytoreductive chemotherapy, tyrosine kinase inhibitors (TKI), or recombinant interleukin-2. The overall response rate was 38% (Table 2). Preventive DLI tended to be more effective than therapeutic one (respectively, 52% *vs* 31%, p=0.08).

Table 2. Efficacy of donor lymphocyte infusions after allo-HSCT

	Efficacy				
Diagnosis	ALL (n=73)	AML+MDS (n=112)	HD (n=16)	NHL (n=20)	CML (n=22)
Overall response rate	38% (28/73)	44% (49/112)	44% (7/16)	45% (9/20)	59% (13/22)
Preemptive DLI (MRD/falling chimer)	52% (13/25)	35% (9/26)	no	2/2	78% (7/9)
Therapeutic DLI (relapse/progression)	31% (15/48)	46% (40/86)	44% (7/16)	39% (7/18)	46% (6/13)

Non-relapse mortality did not differ between children and adults (32% vs. 37%, p>0.2), being also dependent on the pre-transplant disease stage, i.e., 21% and 25% for the 1st remission, 31% and 43%, for the 2nd remission; 50% and 61% for the ≥ 3rd remission (Fig. 8).

Acute GVHD was noted in 34% of patients, including clinically severe complications (grade III to IV) observed in 13.8% of patients. No statistically significant differences in acute GVHD incidence were revealed between the groups of related and unrelated allo-HSCT (p=0.1).

Chronic GVHD after allo-HSCT was evaluated in patients surviving more than 100 days. The incidence of chronic GVHD was 40.9%, including extended clinical forms (33.4%). OS rate among patients with chronic GVHD was 68%, as compared to the patients free of chronic GVHD (52%, p =0.03).

In multivariate analysis, only ALL phenotype (Ph (+) B-ALL and T-ALL vs Ph (-) B-ALL [2.21 (95% CI 1.3-3.4), p=0.05] and acute GVHD [grade 0-1 *versus* grade 2-4: 1.49 (95% CI 0.9-2.8), p=0.04] influenced the RI values.

Discussion

In our study, patient age (children/adults) had no effect on OS, EFS, RI and incidence of GVHD. Disease state at the time of allo-HSCT showed the greatest impact upon OS (47% when transplanted in remission *vs* 18%, in active disease), and upon RI, thus being in accordance with similar results of e.g., F. Hutchinson Cancer Research Center: dis-

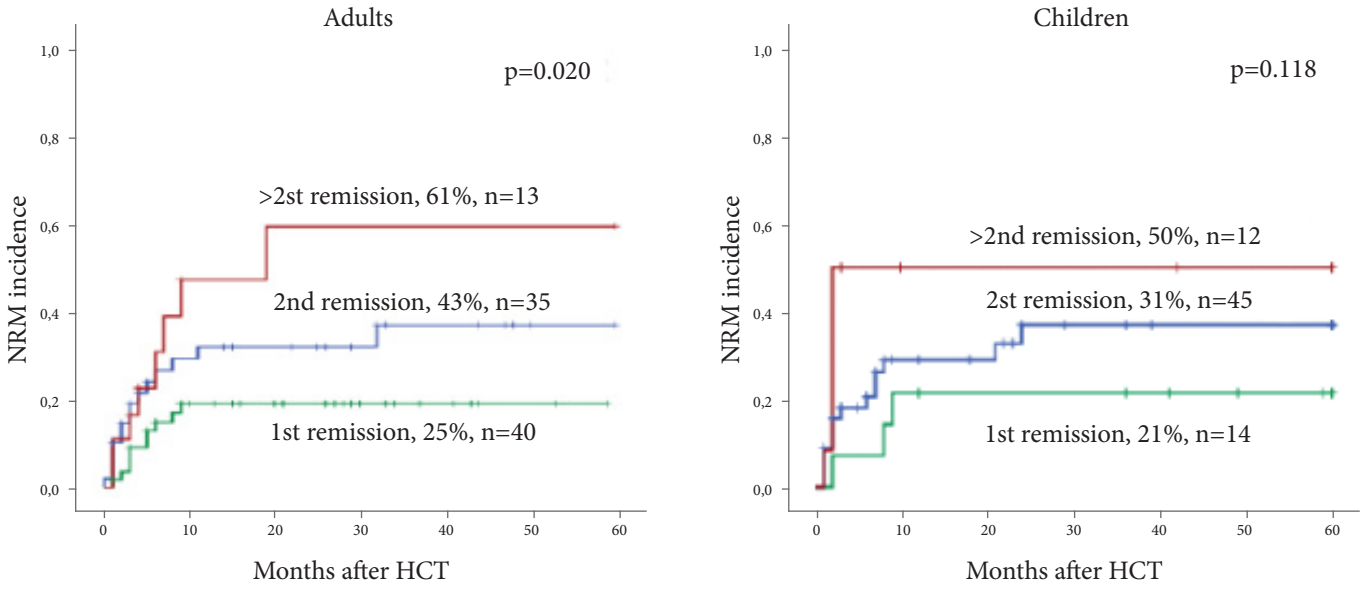


Figure 8. Non-relapse mortality compared in pediatric and adult ALL depending on the disease status before allo-HSCT

ease-free survival was 33% *vs* 9%, and relapse rates – 22% *vs* 45% [5]. The number of previous treatment cycles before allo-HSCT was also of sufficient importance. Both OS overall survival and RI were the highest after HSCT in the 1st remission, with decreased survival for the patients treated in 2nd or 3rd remission, along with lower NRM rates. This trend is in accordance with results obtained by other researchers, where the patients in 1st and in the 2nd remission showed a sufficient difference in relapse risk [6, 10, 18].

More recently, a distinct trend is seen towards allo-HSCT in other ALL patients than those with high-risk cytogenetics. In the study of the Dutch-Belgian HOVON cooperative group, the comparisons were made between the patients with/without available donors. Allo-HSCT has shown to benefit the patients from both high and standard-risk groups. For standard risk group, the OS rates were 69% versus 49% ($p<0.05$) and RI, 14% vs 52% ($p <0.001$). Appropriate levels for the high-risk groups were 53% vs 41% ($p= 0.5$), and 34% vs 61%, $p = 0.03$, respectively [4]. In our study, however, the OS and RI proved to be similar for high and standard-risk ALL.

The disease relapse after allo-HSCT has significant impact upon outcomes. Early detection of the minimal residual disease and/or falling donor chimerism after allo-HSCT, especially in high risk group patients, may be a clinical indication for DLI and/or target therapy (TKI, blinatumomab) [13]. Although DLI has limited benefit in ALL [3, 17], our data demonstrated that preventive DLI may be more effective than therapeutic DLI.

Sufficient HLA-incompatibility between the donor and recipient, both for major and minor antigens, is also known the exert a negative effect on the results of allo-HSCT, by association of severe immunological complications which enhance mortality of patients [8, 20]. It was also confirmed by our results obtained in the groups with different types of HSC donors. Reduced intensity of conditioning regimens did not affect the RI, due to immunoadoptive graft-versus-leukemia effect and usage of donor lymphocyte infusions for prophylactic and preventive purposes [9, 15, 16].

In some patients who had no available HLA-matched donors, the HSCs were taken from haploidentical family members. Most of the patients treated with haplo-HSCT exhibited active malignant disease at the time of allo-HSCT, and the disease progression after allo-HSCT was a main cause of death. Noteworthy, we didn't observe any uncontrolled severe GVHD in this group. In our experience, haplo-HSCT is a promising approach with post-transplant cyclophosphamide used for the GVHD prophylaxis in the patients with very high risk and late relapses. These data correspond to a study published by Bacigalupo et al. [2]. The authors have shown that mortality in this setting was, mainly, due to malignancy relapse (22%), whereas fatal GVHD was diagnosed only in 2%.

Conclusions

Allo-HSCT from an HLA-matched related or unrelated donor is recommended for the patients with high-risk ALL in the 1st remission, and for all patients in the 2nd remission. Due to advent of new drugs (targeted therapy, monoclonal antibodies) the indications for allo-HSCT are constantly changing. In adult patients, a trend for transplantation in the 2nd remission is evident, thus corresponding to appropriate recommendations for children. An additional criterion for allogeneic transplantation is the 1st remission and grafting from HLA-mismatched or alternative donor is a high level of minimal residual disease, thus requiring further research.

Conflict of interest

None declared

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