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Allogeneic stem cell transplantation from HLA-mismatched donors for pediatric patients with acute lymphoblastic leukemia treated according to the 2003 BFM and 2007 International-BFM studies: impact of disease risk on outcomes.

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Summary

Rational: Allogeneic HSCT is beneficial for pediatric patients with relapsed or (very) high-risk ALL in remission. A total of 1115 consecutive patients were included in the ALL SCT 2003 BFM study and the ALL SCT 2007-International study and were stratified according to relapse risk (Standard vs. High vs. Very High Risk of Relapse) and donor type (Matched Sibling vs. Matched Donor vs. Mismatched Donor).

Patients and methods: A total of 148 patients (60% male, median age 8.7 years; B-cell precursor ALL: 75%) were transplanted from MMD, which was defined as either less than 9/10 HLA-compatible donors or less than 5/6 unrelated cord blood after myelo-ablative conditioning regimen (TBI-based: 67%) for HRR (n=42) or VHRR disease (n=106). The stem cell source was either BM (n=31), unmanipulated PBSCs (n=28), T-cell ex vivo depleted PBSCs (n=59) or cord blood (n=25). The median follow-up was 5.1 years.

Results: The 4-year OS and EFS was 56±4% and 52±4%, respectively, for the entire cohort. Patients transplanted from MMD for HRR disease obtained remarkable 4-y OS and EFS values of 82±6% and 80±6%, respectively, while VHRR patients obtained values of 45±5% and 42±5% ($p<0.001$), respectively. The cumulative incidence of relapse was 29±4%, and that of NRM was 19±3%. The cumulative incidence (CI) of limited and extensive cGVHD was 13±3% and 15±4%, respectively, among the 120 patients living beyond D100. Multivariate analysis showed that OS was lower for transplanted VHRR disease patients ($p=0.002$, HR 3.62, 95%CI 1.60-8.20) and for patients beyond CR2 vs CR1 ($p<0.001$; HR: 3.68, 95%CI: 1.79-7.56); relapse occurred more frequently in patients with VHRR disease ($p=0.026$; HR: 3.30, 95% CI: 1.16-9.60) and for those beyond CR2 ($p=0.005$; HR: 4.16, 95% CI: 1.52-10.59). NRM was not significantly higher for CMV-positive recipients receiving CMV-negative grafts ($p=0.12$; HR: 1.96, 95% CI: 0.84-4.58).

Conclusion: HSCT with a mismatched donor is feasible in pediatric ALL patients but

leads to inferior results compared to HSCT with better matched donors, at least for patients transplanted for VHRR. The results are strongly affected by disease status. The main cause of treatment failure is still relapse, highlighting the urgent need for interventional strategies after HSCT for patients with residual leukemia before and/or after transplantation

Introduction

Approximately 80% of pediatric patients presenting with acute lymphoblastic leukemia (ALL) diagnosed above the age of 1 year are currently treated with conventional polychemotherapy protocols[1, 2]. However, approximately 10% of patients present with poor prognostic features at initial diagnosis, and 20% of ALL pediatric patients eventually relapse after first complete remission (CR1). Additional therapy is required for patients who achieve complete remission (CR) One option is allogeneic stem cell transplantation (HSCT)[3-6].

The overall results of HSCT have consistently improved over time through the reduction in non-relapse mortality. The use of unrelated volunteer donors, unrelated cord blood or haploidentical donors makes HSCT feasible for every patient. Unfortunately, the relapse incidence has not changed and remains a substantial concern.

In many countries, the number of allogeneic HSCTs from non-sibling donors has exceeded that of MSD-HSCT since the middle of 2005[7]. In 2015, Peters et al published the results obtained by the BFM group for pediatric patients with ALL in CR. In that publication, the authors demonstrated the equivalence of the results obtained with matched sibling donors (MSD) and with matched unrelated donors (MD). [8]. The International BFM consortium reproduced these results in the I-BFM ALL HSCT 2007 study (paper in preparation). In both studies, patients were allocated to different relapse risk groups. Patients with a very high relapse risk (see table 1) were eligible for any donor type and available stem cell source.

Here, we report the outcomes of 148 patients who were transplanted in first or subsequent CR from an HLA-mismatched donor (MMD) whatever the per protocol disease risk allocation.

Patients and Methods

Transplant centers from 3 countries (Austria, Germany, and Switzerland) participated in the 2003 BFM ALL study from 2003 to 2011, and 10 additional countries (Czech Republic, Denmark, France, Israel, Italy, the Netherlands, Poland, Sweden, Slovakia, and Turkey) participated in the International BFM ALL SCT 2007 study from 2007 to 2011. Both studies were prospective, multicenter open trials (extended as a register studies until 2013), approved through the central and local ethics committees Informed consent was obtained from legal guardians and from patients when possible prior to study entry.

Inclusion Criteria. All consecutive patients up to the age of 18 years at the time of initial ALL diagnosis or relapse with an indication for allogeneic HSCT according to national frontline and relapse protocols were eligible for the present study, Complete remission was defined based on bone marrow (BM) with active hematopoiesis and fewer than 5% leukemic blast cells (identified morphologically) and normal cerebrospinal fluid.

Donor type. HLA-mismatched donors (MMDs) were defined as donors with more than one (>9/10) or more allelic or antigenic disparities up to a different haplotype (MMD), regardless of relationship. Unrelated cord blood was also accepted as a stem cell source. HLA typing was defined using low-resolution molecular techniques for HLA-A and HLA-B and high resolution typing for HLA-DR, and less than 5/6 matches were classified as MMD.

Risk stratification. The patients were stratified according to BFM eligibility criteria for transplantation: standard relapse risk (SRR) patients were not eligible for any HSCT, high relapse risk (HRR) patients were eligible for either MSD or MD HSCT, and very high relapse risk (VHRR) patients also had indication for MMD transplants.

Indication for allogeneic HSCT according to BFM-frontline protocols:

Risk definition and indications for allogeneic hematopoietic stem cell transplantation were summarized in both table 1a and 1b for patients in CR1 and CR2, respectively. Briefly, stratification was based on prednisone response, some fusion-transcripts or gene abnormalities and MRD level at time-point 2 (i.e. day 80) in CR1 and T versus B-cell lineage plus delay from first remission for patients in CR2.

The MRD levels just before transplantation procedure as well as at defined time-point post transplantation were not neither mandatory nor registered.

Stem cell source. Bone marrow (BM) was the recommended source according to the protocol, but granulocyte colony-stimulating factor-primed peripheral blood (PB) and cord blood (CB) stem cells were also acceptable sources, according to transplant or donor center preference. Target doses of $>3x10^8$ nucleated cells (NC)/kg recipient body weight and $>1.5x10^6$ $CD34^+$ cells/kg recipient body were recommended for both BM and PBSC. For CB, the target doses were $3x10^7$ nucleated cells (NC)/kg recipient body weight and $>1x10^6$ $CD34^+$ cells/kg recipient body.

Transplant procedure. A consistent myeloablative conditioning regimen was performed depending on both recipient age and donor type and did not depend on disease risk group. For patients in the present study, i.e., those transplanted from MMD and older than 2 years of age (except for 8 patients < 2 y), the conditioning regimen was based on hyper-fractionated total body irradiation (TBI, dose 1200 and 200 cGy bid on days -10 to -8), fludarabine (40 $mg/m^2/d$ for 4 days from D-7 to D-4) and etoposide (40 mg/kg at D-3). Patients younger than 2 years of age received body-weight adjusted doses of either IV or oral busulfan from D-11 to D-8, followed by fludarabine (40 $mg/m^2/d$ from D-7 to D-4) and cyclophosphamide (60 mg/kg for 2 days, D-3 and -2).

GVHD prophylaxis comprised cyclosporine-A, methotrexate and anti-thymocyte globulin (ATG Fresenius 20 mg/kg/dose, on days -4, -3, -2). Methotrexate was substituted with steroids in CB recipients. Allowing protocols and up to the physician/center decision, some patients received ex vivo T-cell depleted grafts either by CD34 positive selection or CD3/CD19 depletion.

Acute and chronic GVHD were graded as previously described. Patients who were alive and in remission 100 days after HSCT were considered at risk for chronic GVHD. The discontinuation of immunosuppression was considered the absence of GVHD.

Statistical Analysis. For non-time to event variables, Chi-Square tests, or where appropriate Fisher's exact test, were used to compare groups for categorical variables, and the Wilcoxon rank-sum test (Kruskal-Wallis test for more than two populations) was used for continuous variables. The overall survival (OS) and event-free survival (EFS) probabilities were calculated using the Kaplan-Meier method, and the groups were compared using the log-rank test. For OS, death resulting from any cause was defined as an event, and for EFS, the events included relapse, secondary malignancy and death of any cause. The starting point for survival analysis was the date of the first HSCT. Survivors were censored at the last follow-up.

The cumulative incidence of chronic GVHD, relapse (CIR) and death in remission, defined as non-relapse mortality (NRM), were estimated using the Kalbfleisch and Prentice approach [9], considering competing risks, which included death in remission and relapse for GVHD, death in remission for CIR, relapse for NRM, and secondary malignancy for all case types described above. Comparisons were made according to the Gray test [10].

The variables included into the multivariate models are patient disease and donor characteristics possibly associated with the defined outcomes according current knowledge

(i.e. age of patient, gender match, stratification group according the risk of relapse, remission status at time of SCT, disease cytomegalovirus (CMV) serostatus, stem cell source and conditioning regimen).

For multivariable analyses, we used logistic regression to model the impact of risk factors on the incidence of aGVHD (data not censored until 100 days after HSCT). The impact of prognostic factors on EFS and OS was evaluated using the Cox proportional hazards model with time-dependent covariates, and the impact on chronic GVHD, CIR and NRM was evaluated using the Proportional Subdistribution Hazards model of Fine and Gray for censored data subject to competing risks [11]. The impact of acute and chronic GVHD on OS, EFS, CIR and NRM was assessed by means of separate Cox (OS, EFS) and Fine and Gray (CIR, NRM) models, including GVHD as a time depending covariate and adjusting for the variables mentioned above.

All p-values below 0.05 were considered significant. The statistical analysis was performed using SAS version 9.4 (SAS Institute, Cary, NC).

All transplant patients were subjected to general analyses, but only patients transplanted from MMD were reported here.

Between 2003 and 2013, 1115 patients, up to the age of 18 years, presenting with ALL in first or subsequent complete remission (CR) were enrolled in either the ALL SCT 2003 BFM Study (n=705) or the ALL SCT 2007 Int BFM Study (n=410). Among these patients, 148 underwent HSCT from MMD, 86 were enrolled in the 2003 BFM study, and the 62 remaining patients were enrolled in the international protocol.

Data regarding patients treated along ALL SCT 2003 BFM study and ALL SCT 2007 Int BFM Study and transplanted from named MSD and MD (as defined per protocol) were published by

Peters et al in Journal of Clinical Oncology in 2016. We did not perform statistical comparison between the cohort reported by Peters et al and the cohort described here.

Follow-up was updated as of May 25, 2016, for patients enrolled in the 2003 BFM ALL study and as of November 15, 2016, for patients enrolled in the International BFM ALL SCT 2007 study.

Results:

The median observation time was 5.1 years for the 148 patients evaluated in the present study. According to the protocol, 106 patients belonged to the very high-relapse risk (VHRR) group (71 patients in the 2003 study and 35 patients in the 2007 study), whereas 42 patients were transplanted from MMD because of high-relapse risk (HRR) disease, meaning that 106 patients received HSCT as per protocol where the 42 others were transplanted up to the physician decision. The patient characteristics are shown in table 1. Briefly, there were 89 males and 59 females (sex ratio: 60.1%). A total of 107 patients presented with B-cell lineage ALL, and 12 and 6 patients suffered from either Ph-positive or MLL-AF4 ALL, respectively. The median age at HSCT was 8.7 years (range: 0.8-20.6), and 88 patients below the age of 10 years were transplanted. A total of 59 patients were transplanted in CR1, 62 patients were transplanted in CR2, and 27 patients were transplanted in CR>2. Ninety-six patients received a TBI-based conditioning regimen, and 97 patients received grafts from unrelated donor. Thirty-three male recipients were transplanted from a female donor. The stem cell sources were ex vivo T-cell depleted peripheral stem cells (PBSCs) for 59 patients, unmanipulated PBSCs for 28 patients, unmanipulated bone marrow for 31 patients, and cord-blood for 25 patients. Twenty-seven CMV serological-positive patients received transplants from CMV serological-negative donors. GvHD prophylaxis was performed according to protocols for

patients transplanted with unmanipulated grafts. Ten patients received CSA +/- MTX in addition to ex vivo T-cell depletion. (Table 2).

A comparison of patients transplanted for VHRR disease with those transplanted for HRR disease revealed no statistically significant difference in donor age, sex-match, stem cell ex vivo T-depletion, ALL phenotype (T-cell lineage vs. B-cell lineage), CMV status match or TBI versus non-TBI-based conditioning regimen. There were more patients with advanced disease in the VHRR group (p=0.007) (Table 3).

Engraftment:

One hundred and thirty-five patients reached neutrophil counts above $0.5x10^9$/l within a median time of 16 (range: 8-70), 26 (range: 12-41) and 27 (range: 12-84) days for PBSCs, BM and CB, respectively.

A total of 114 and 100 patients reached platelet counts above $20x10^9$ and $50x10^{e9}$/l, respectively. The median time to reach more than $50x10^9$/l platelets was 22 (10-78), 34 (18-54) and 62 (11-142) days for PBSCs, BM and CB, respectively.

A total of 9 patients died before leukocyte engraftment.

Graft versus *host disease:*

Seventy-nine patients did not develop any acute GvHD above grade 1, 32 patients experienced grade 2 aGvHD, and 15 exhibited grade 3 to 4 aGvHD. The cumulative incidence of grade 2-4 aGvHD was 33%.

Multivariate analysis revealed that only remission status had a significantly negative impact on the occurrence of grade 3 to 4 aGvHD. Neither donor age, sex-match, GvHD prophylaxis, patient age nor TBI showed any statistically significant impact.

Among the 120 patients who survived after D100 and were subsequently evaluated for chronic GvHD, 16 experienced extensive cGvHD. The 2-year CI of limited and extensive cGvHD was 13±3% and 15±4%, respectively.

In multivariate analysis, none of the risk factors (HSCT indication, age and gender of donor, disease status at HSCT, GvHD prophylaxis, TBI in conditioning regimen and patient's age) had statistically significant impact on cGVHD (limited and extensive) or on extensive cGVHD alone.

Overall survival:

The 4-year overall survival was 56±4% for the entire cohort of 148 patients, with a trend for better results in the international 2007 study compared to in the 2003 BFM study (64±6% vs. 50±6%, p=NS) (Supplemental Appendix Figure S2). Univariate analysis revealed that HSCT for VHRR versus HRR disease resulted in worse survival (45±5% vs. 82±6%, p<0.001). Similarly, HSCT in CR1 or CR2 versus CR>2 was a favorable prognostic factor (71±6% vs. 53±6% vs. 27±9%, p<0.0001) (Figure 1).In a multivariate analysis considering indication, disease status at HSCT, D/R CMV status, GvHD prophylaxis, TBI in the conditioning regimen and patient's age as risk factors for OS, VHRR disease was associated with a statistically significantly worse OS(p=0.002; HR:3.62, 95%CI: 1.60-8.20). HSCT for advanced disease (CR>2 vs CR1) (p<0.001; HR: 3.68, 95%CI:1.79-7.56) and transplantation from a CMV-negative donor to a CMV-positive patient (p=0.028; HR: 1.99, 95%CI:1.08-3.66) were also negative prognostic factors. An additional multivariate analysis did not reveal statistically significant impact of aGVHD of any grade or aGVHD of grade 3 and 4 on OS (Supplemental Table S6) .

Event-free survival:

The 4-year EFS was 52±4% for the entire cohort of 148 patients. One patient developed a secondary myelodysplatic syndrome. No other secondary malignancies were reported up to the date of point.

As for OS, univariate analysis revealed that HSCT for VHRR versus HRR disease resulted in worse outcomes (42±5% vs. 80±6%, p<0.001). Similarly, transplantation in CR1 or CR2 versus CR>2 was a favorable prognostic factor (66±6% vs. 50±6% vs. 27±9%, p<0.001).

In a multivariate analysis adjusted for indication, disease status at HSCT, D/R CMV status, GvHD prophylaxis, TBI in the conditioning regimen and patient age, HSCT for VHRR disease (p=0.002; HR:3.33, 95%CI: 1.55-7.16), and HSCT for advanced disease (p<0.001; HR: 3.55, 95%CI:1.76-7.16) were statistically significant negative prognostic factors. An additional multivariate analysis did not reveal statistically significant impact of aGVHD of any grade or aGVHD of grade 3 and 4 on EFS (Supplemental Table S6).

Relapse incidence

In univariate analysis, remission status appeared to be a strong prognostic factor for relapse with 4-year CI of 17±6%, 31±6% and 49±10% for patients transplanted in CR1, CR2 and CR>2, respectively (p=0.003).

In multivariate analysis adjusted for HSCT indication, disease status at HSCT, GvHD prophylaxis, D/R CMV status, TBI in the conditioning regimen and age of patient, and HSCT for VHRR disease appeared to be statistically significant negative prognostic factors (p=0.026; HR: 3.33, 95%CI: 1.16-9.60), and HSCT for more advanced disease was also a negative prognostic factor (CR>2 vs. CR1 p=0.005; HR: 4.02, 95%CI: 1.52-10.59).

In an additional multivariate analysis no statistically significant impact of aGVHD of any grade or aGVHD of grade 3 and 4 on the relapse incidence was reviled. There was a significant positive impact of chronic GVHD on relapse incidence when limited and

extensive cGVHD were considered all together but this impact disappeared when limited or extensive cGVHD were considered separately.

Non-relapse mortality (NRM)

The 4-year CI of NRM was 19±3% without any difference between both studies.

Univariate analysis revealed that the combination of CMV-negative donors with CMV-positive recipients had a negative impact on NRM of borderline significance: 4-year CI of NRM was 30±9% vs. 15±3% (p=0.053). Remission status appeared to be a strong prognostic factor for NRM with 4-year CI of 17±6% %, 19±5% and 24±9% for patients transplanted in CR1, CR2 and CR>2, respectively.

Multivariate analysis adjusted for HSCT indication, disease status at HSCT, GvHD prophylaxis, TBI in conditioning regimen and age of patient showed that none of these factors were significant. Similarly, the negative impact of the combination of CMV-negative donors with CMV-positive recipients reached only borderline significance (p=0.12, HR=1.96; 95%CI: 0.84-4.58). In an additional multivariate analysis aGVHD of any grade was associated with higher NRM (p=0.002, HR=3.35, 95%CI: 1.19-9.43).

Discussion:

Allogeneic HSCT has represented the best available treatment for pediatric patients suffering from poor-risk malignant hematological diseases in general and particularly those with poor-risk acute lymphoblastic leukemia [3-5, 8, 12-15]. The progress achieved in both conventional chemotherapy and stem cell transplantation techniques has augmented the potential for a cure, particularly after MSD- and MD-HSCT.

High molecular class 1 and 2 HLA typing completely changed the ability to identify full-matched donors defined as 8/8 (HLA A, B, C and DR) or 10/10 (same + DQB1) HLA-

compatible donors in North America and Europe, respectively. Moreover, at least in pediatric patients with malignant diseases, the use of unrelated compatible donors was integrated into treatment algorithms for poor-risk conditions. The ability to use partially matched unrelated cord blood completed the repertoire of potential stem cell sources. However, HSCT from alternative donors – whether related or unrelated - remained associated with high treatment failure rates, reflecting both non-relapse mortality and relapse. Thus, such alternative HSCT is often limited to high risk patients and to some experienced centers able to perform ex vivo graft manipulations, such as T-cell depletion through either positive $CD34^+$-cell selection or $CD3^+ \pm CD19^+$-cell depletion [14, 16-19]. However, these disappointing results were mainly described from retrospective and single-center studies and should be cautiously interpreted. In 2003, the Austrian-German-Swiss BFM protocol initiated a prospective study to evaluate the feasibility of the systematic use of either 9 or 10/10 unrelated donors for patients < 18 years old with an indication of allogeneic HSCT for ALL in first or subsequent CR. The results demonstrated the equivalence between MSD and MD, regardless of the disease relapse risk[8]. The 4-year OS was 79±4% and 73±3% for patients transplanted from MSD and MD, respectively (p=NS). Both 4-year EFS and relapse CI were also similar in both groups. NRM was statistically better in the MSD-group. This initial study was followed by an international study of 10 countries, and the global results were similar (Balduzzi et al, submitted). Both studies included also patients without an MSD or MD donor to provide a common platform of therapy.

If minimal residual disease level at the end of induction and of consolidation, in first as well as in second line therapy was part on the disease risk stratification, MRD levels were not registered just before and after HSCT. However, both protocols BFM-2003 and IBFM-2007 lead to better describe this specific pediatric population.

Here, we report the results of these two prospective studies on 148 HRR and VHRR patients transplanted from MMD for ALL in first or subsequent remission. Both 4-year OS and EFS (56±4% and 52±4%) were inferior to the results reported within the same studies for patients with better-matched donors. However, the results remained remarkable and satisfying for HRR-patients transplanted from MMD with 4-year OS and EFS of 82±6% and 80±6%, respectively. These results seem to be comparable to those reported by Peters et al among HRR patients transplanted from either MSD or MD along the same protocols. The overall results were better than those recently published by a French group on the comparisons between transplantation from one and two CB units in patients with acute leukemia[20]. However, in this paper, it was not possible to depict patients transplanted with either MD or MMD neither for HRR or VHRR disease as defined in our current study. Indeed, a strong comparison appears as hazardous.

In the present study, relapse was the main cause of failure, higher than NRM, consistent with the literature. In a 25-year retrospective study, Mateos et al showed a static relapse incidence over this period whilst TRM reduced significantly during the same time[21]. In the paper about SCT-BFM 2003 trial, Peters et al reported a CI of relapse from of 22-24% in patients transplanted from either sibling or unrelated matched donor[8]. Mo et al reported same results when describing transplantation from either haplo-identical donor or unrelated cord blood transplantation[22]. And finally Michel et al reported as well 14.9 to 23.4% CI of relapse in the French randomized trial comparing transplantation from either one or two cord blood unit in patients below 35 years with leukemia[23]. However, two-fold higher transplant-associated deaths were observed in patients transplanted from MMD compared to those transplanted from MSD and MD donors. Relapse represents the most important challenge to address. The options to reduce post-transplant relapse incidence currently include the better determination of peri-transplant measurable residual disease, tailored chemotherapy and

immunomodulation. We were able to analyze the impact of relapse risk and disease status on the end-points. Both factors appeared statistically adverse for OS, EFS and relapse incidence, indicating the need for developing new approaches for VHRR. Based on these results, it is likely mandatory and safer to perform HSCT in CR1 or CR2 and not wait for further relapse. Here, we presented our experiences with MMD-HSCT for patients with VHRR and HRR who were uniformly pretreated with BFM/IBFM-frontline protocols and a harmonized transplant procedure. These findings showed a good outcome for CR1+ CR2, and HRR patients. Nevertheless, there was a high rate of treatment failure for patients beyond CR2 or patients with VHRR, and the source of mismatched stem cells did not influence this outcome.

For VHRR patients, the introduction of new agents and techniques, such as bi-specific antibodies or Chimeric Antigen Receptor-T cells, may represent progress in decreasing relapse rates and non-relapse-mortality if they allow HSCT to be performed at an earlier stage[24-28]. The optimal timing for using these new tools, before or after transplantation, for positive MRD and before overt relapse remains undefined. Obtaining significantly less transplant associated early and late toxicity is also desired.

Thus, we avoided TBI-based conditioning regimen for patients below 2 years with MMD. To further investigate the possibility of TBI-free conditioning regimen, we initiated a prospective randomized trial (Eudract N° 2012-003032-22, see also www.clinicaltrials.gov) to evaluate the outcome after TBI- versus chemo-based conditioning regimens in patients above 4 years of age, with ALL and MSD or MD. All other patients (younger than 4 years and those with only MMD, including T-repleted post-transplant cyclophosphamide haploidentical HSCT patients) receive TBI-free conditioning regimens.

In the present study, we demonstrated the feasibility of allogeneic HSCT from alternative donors in both HRR and VHRR pediatric patients with ALL in complete remission after

myelo-ablative conditioning. Our findings show good outcomes for HRR patients in CR1 or CR2. These results demonstrate the feasibility of using MMD in HRR patients with acceptable results. In HHR patients, MMD seem offer the same chance of success as using better HLA-matched donors. However, further progress is needed to decrease overall treatment failure, i.e., both relapse rate and treatment-related mortality in VHRR patients.

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Figures and Tables:

Figure 1: 4-year Overall Survival (OS) and Event Free Survival (EFS)

Figure 2: 4-year Cumulative Incidence of Relapse (CIR) and Non Relapse Mortality (NRM)

Table 1: Risk definition and indications for allogeneic HSCT in ALL according to the BFM criteria; a. in CR1 b. after first relapse

Table 2 : Main characteristics of patients

Supplemental Appendix

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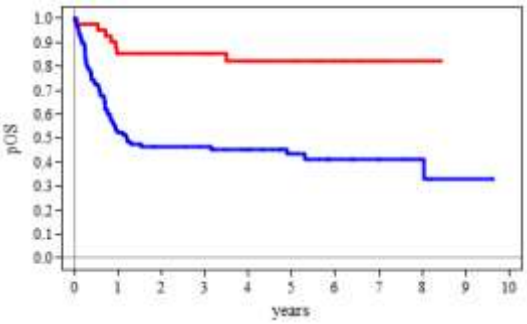
Figure 1

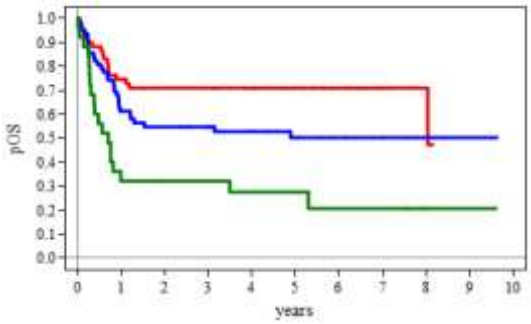
A. Overall Survival (OS) according indication
B. Overall Survival (OS) according remission status at HSCT
C. Event Free Survival (EFS) according indication
D. Event Free Survival (EFS) according remission status at HSCT

A



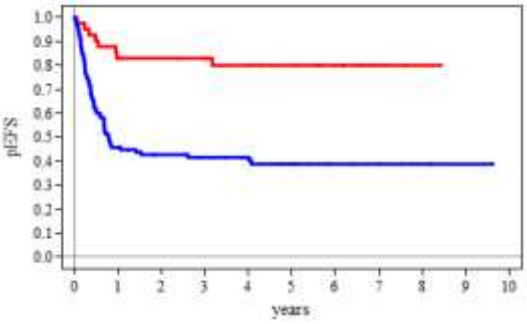
	Patients	Events	4 years - pOS	p-value
High Relapse Risk (HRR)	42	7	0.82±0.06	<0.001
Very High Relapse Risk (VHRR)	106	60	0.45±0.05	

B



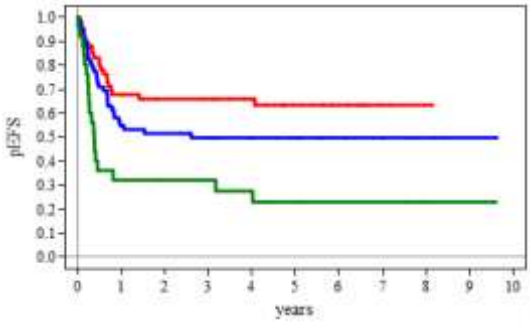
	Patients	Events	4 years - pOS	p-value
CR1	59	18	0.71±0.06	<0.0001
CR2	62	30	0.53±0.06	
CR>2	27	19	0.27±0.09	

C



	Patients	Events	4 years - pEFS	p-value
High Relapse Risk (HRR)	42	8	0.80±0.06	<0.001
Very High Relapse Risk (VHRR)	106	63	0.42±0.05	

D

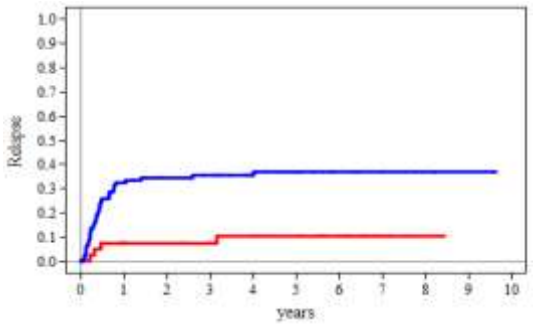


	Patients	Events	4 years - pEFS	p-value
CR1	59	21	0.66±0.06	<0.0001
CR2	62	31	0.50±0.06	
CR>2	27	19	0.27±0.09	

Figure 2

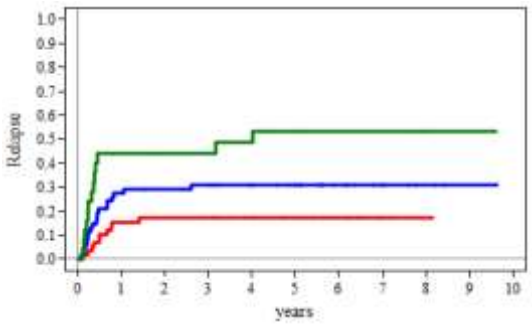
A. Cumulative Incidence of Relapse (CIR) according indication
B. Cumulative Incidence of Relapse (CIR)according remission status at HSCT
C. Non Relapse Mortality (NRM) according indication
D. Non Relapse Mortality (NRM) according remission status at HSCT

A



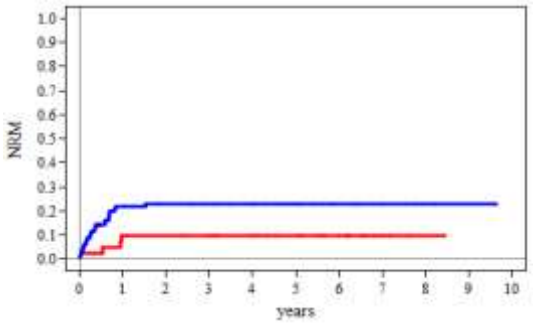
	Patients	Events	4 y. CI Relapse	p-value
High Relapse Risk (HRR)	42	4	0.10±0.05	0.002
Very High Relapse Risk (VHRR)	106	38	0.36±0.05	

B



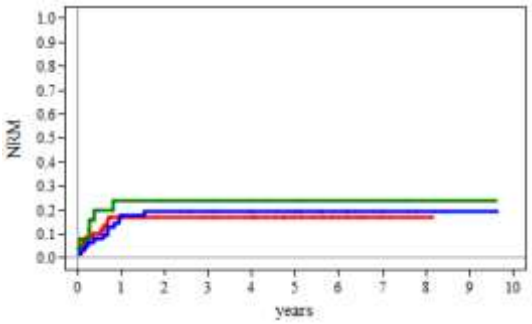
	Patients	Events	4 y. CI of Relapse	p-value
CR1	59	10	0.17±0.05	0.003
CR2	62	19	0.31±0.06	
CR>2	27	13	0.49±0.10	

C



	Patients	Events	4 y. CI Relapse	p-value
High Relapse Risk (HRR)	42	4	0.10±0.05	0.065
Very High Relapse Risk (VHRR)	106	24	0.23±0.04	

D



	Patients	Events	4 y. CI of NRM	p-value
CR1	59	10	0.17±0.05	0.745
CR2	62	12	0.19±0.05	
CR>2	27	6	0.24±0.09	

Table 1 : Risk definition and indication for allogeneic HSCT in ALL according to the BFM criteria.

A. In CR1
B. Beyonf
   D CR1

Indictaion for allogeneic stem cell transplantation in ALL in CR1 according to the BFM criteria

Amendement 10.10.2008		PCR-MRD Results				
		MRD-SR	MRD-MR	MRD-HR		No MRD result
				MRD-TP2≥10^{-3}	MRD-TP2≥10^{-2}	
HR by MRD only (MRD at TP2≥10^{-3})		n.a.	n.a.	MSD/MD	MSD/MD/MMD	n.a.
HR criteria (in hierarchical order)	No CR d33	n.a.	MSD/MD/MMD	MSD/MD/MMD	MSD/MD/MMD	MSD/MD/MMD
	PPR + (9;22)	MSD/MD/MMD	MSD/MD/MMD	MSD/MD/MMD	MSD/MD/MMD	MSD/MD/MMD
	PPR + (4;11)	MSD/MD	MSD/MD	MSD/MD	MSD/MD/MMD	MSD/MD
	PGR + (9;22)	No	MSD/MD	MSD/MD	MSD/MD/MMD	MSD/MD
	PGR + (4;11)	MSD	MSD	MSD/MD	MSD/MD/MMD	MSD
	PPR + *	No	No	MSD/MD	MSD/MD/MMD	MSD/MD
	"Favourable PPR"#	No	No	MSD/MD	MSD/MD/MMD	No

MSD= Matched sibling Donor; MD: Marched donor; MMD: Mismatched donor; no = no SCT indicated; N.a. = not applicable
PPR = Poor prednisone response ; GPR: Good prednisone response; WBC: White blood cell count at diagnosis: NRd33: No remission at day 33; MRD: Minimal Residual Disase
*PPR + pro-B ALL or T-ALL and/or M3 D15 and/or WBC > 100.000/µl
#PPR + none of the above criteria
MRD-SR: MRD negativity after 4 and 12 weeks induction treatment, measured with at least one target with a sensitivity of ≤10^{-4}
MRD-MR: any MRD positivity after 4 and 12 weeks induction treatment, but ≤10^{-3} at week 12 (TP2)
MRD-HR: MRD ≥10^{-3} at week 12 (TP2)

Indications for allogeneic SCT in ALL according to "Interfant 06": age at diagnosis below 6 moonths plus MLL rearrangement plus initial WBC ≥ 300.000/µl

Table 2 : Patient characteristics

		Patients (Total)		HRR (High Relapse Risk)		VHRR (Very HighRelapse Risk)		p-value
Total	**N**	148		42		106		
Age of patient at SCT	Median (range)	8.7 (0.8-20.6)		7.5 (0.8-17.7)		8.9 (1.0-20.6)		
<= 4 years	**N**	24	16%	7	17%	17	16%	0.758
>4 and <=10 years	**N**	64	43%	20	48%	44	42%	
>10 years	**N**	60	41%	15	36%	45	42%	
Age of donor				0				
<= 18 years	**N**	27	20%	8	20%	19	19%	0.207
>18 and <=35 years	**N**	38	28%	15	38%	23	23%	
>35 years	**N**	73	53%	17	43%	56	57%	
missing	**N**	10		2		8		
Gender donor/patient								
donor-female, patient-male	**N**	33	23%	9	21%	24	24%	0.8238
others	**N**	111	77%	33	79%	78	76%	
missing	**N**	4				4		
Remission status at SCT				0				
CR1	**N**	59	40%	23	55%	36	34%	0.007
CR2	**N**	62	42%	17	40%	45	42%	
CR>2	**N**	27	18%	2	5%	25	24%	
Phenotype of patient				0				
b-cell	**N**	107	75%	30	71%	77	77%	0.859
t-cell	**N**	32	23%	11	26%	21	21%	
other	**N**	3	2%	1	2%	2	2%	
not available	**N**	2		0		2		
missing	**N**	4		0		4		
Graft source/manipulation				0				
BM unmanipulated	**N**	31	22%	11	26%	20	20%	0.216
PB unmanipulated	**N**	28	20%	11	26%	17	17%	
CB unmanipulated	**N**	25	17%	8	19%	17	17%	
ex vivo manip. PB	**N**	59	41%	12	29%	47	47%	
gtaft manipilation data missing	**N**	5		0		5		
CMV status donor/patient								
donor-negative, patient-positive	**N**	27	19%	7	17%	20	20%	0.6321
others	**N**	113	81%	34	83%	79	80%	
not tested		2		1		1		
missing	**N**	6				6		
TBI				0				
no	**N**	47	33%	12	29%	35	35%	0.694
yes	**N**	96	67%	30	71%	66	65%	
missing	**N**	5		0		5		