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Outcome and prognostic factors for pediatric patients receiving an haploidentical transplantation using CD3/CD19 depleted grafts

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Abstract

Since 2005 to December 2014, 75 children with hematological malignancies underwent a total of 70 haploHSCT using CD3+/CD19+ depletion for PBPC manipulation. Nineteen patients were in 1st CR, 30 in 2nd CR and 26 were in >2nd CR or persistent disease. The conditioning regimen consisted of i.v. fludarabine, busulfan and thiotepa. Allografts contained a median of 7.29 x10^6 CD34 cells/kg and 1.0 x 10^4 CD3 cells/kg. Median times to neutrophil and platelet recovery were 13 and 10 days, respectively. The probability of severe aGvHD and cGvHD (any grade) were 18±5% and 46±7% respectively. NRM was 10±4% by day +100 and 23±5% by 2 years after transplant. Causes of dead were relapse in 13 cases, viral infections in 8, microangiopathy in 3, graft failure in 1 and others in 2. The probability of relapse was 32±6%. With a median follow-up of 22 months, the probability of DFS was 52±6%. On a multivariate analysis the factors that positive impact on DFS were age below 12 years (HR: 2.18, p=0.04), cGvHD (HR: 2.56, p=0.045), early disease status (HR: 8.30, p=0.04) and donor KIR B Haplotype (HR: 2.59, p= 0.01). Our results suggest that haploidentical donors are a good option for pediatric patients with high-risk hematological malignancies who need an allogeneic transplantation. Graft manipulation resulted on low incidence of severe aGvHD. NRM was higher in patients over 12 years. DFS was better for patients in early phase of disease, using KIR B haplotype donors and with cGvHD mainly due to lower relapse incidence. Severe viral infections is a relevant problem in the early phase after transplantation.

Background

Nowadays, haploidentical hematopoietic stem cell transplantation using T-cell depleted grafts is an option for pediatric patients with hematological malignancies in need an allogeneic transplantation and lacking an HLA-identical donor.
CD3/CD19 depletion as graft manipulation method retains large numbers of important immune cells in the graft as well as "unaltered" CD34+ .
However, few papers have been reported addressing pronostic factors and outcomes.

Transplants (n=75)

Patients (n=70)

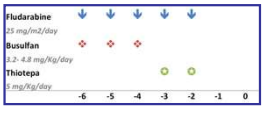
Age	9 years (6 months- 19 years)
Gender	48 male/ 27 female
Weight (Kg)	30 (6-76)
Lansky (%)	90 (60-100)
Diagnosis	
ALL	38
AML/MDS/JMML	37
Disease status:	
- 1st CR	19
- 2nd CR	30
- >2nd CR	12
- Not in remission	14
Transplant number	
1st	51
2nd	22
3rd	2
Median follow-up	22 months (3-108)

Donors

Age (years)	40 (2-54)
Gender	25 male/ 50 female
Mother/Father/Brother	48/19/8
KIR match	35 y / 30 n
KIR haplotype	19 A/ 56 B
Cell composition	
- CD34+ x 10^6/kg	7.02 (1.19-41.6)
- CD3+ x 10^3/kg	10.5 (1.0-11.8)
- CD56+ x 10^6/kg	24.6 (2.57-141.3)

Methods

Since 2005 to 2014, pediatric patients diagnosed of high-risk hematological malignancies with transplantation criteria and "good" clinical condition were included in the study protocol.
Patients do not have time to be waiting for searching a high resolution MUD or lack a MRD or MUD.
Primary "endpoint" is disease-free survival and factors affecting DFS.
Secondary "endpoints" are engraftment kinetics, immune reconstitution, NRM and relapse incidence.
Univariate and multivariate analyses were performed using log-rank test and Cox regression model.
Pediatric patients were conditioned with fludarabine, busulphan and thiotepa regimen.



Donors were mobilized with filgrastim (10 µg/kg/day x 4 days).
Donors PBPCs were collected using the Cobe Spectra cell separator (Terumo BCT) .
CD3+/CD19+ depletion was performed using the CliniMacs (Miltenyi Biotec) device.
The final cellular product was infused fresh on day 0.

Results

Hematopoietic engraftment

Days to neutrophil engraftment	13 (7-21)
Days to platelets ≥ 20 x 10^3	10 (5-70)
Days to platelets ≥ 50 x 10^3	13 (5-150)
Days to platelets ≥ 100 x 10^3	15 (5-270)

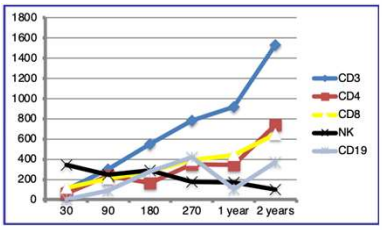
Supportive care

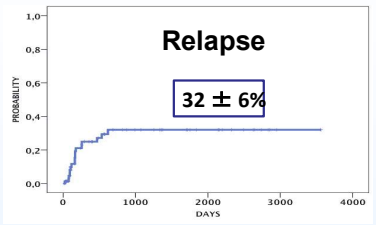
Red blood cells days	2 (0-21)
Platelets days	3 (0-40)
Parenteral nutrition days	0 (0-40)
Fever days	1 (0-15)
Antibiotic days	12 (0-40)
Hospitalization days	15 (10-41)

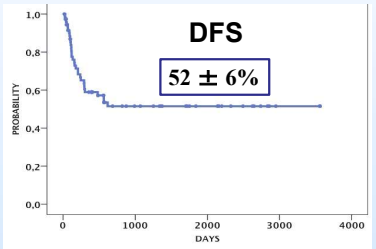
Complications

Acute GVHD (any grade)	36 ± 6%
Chronic GVHD	46 ± 7%
Graft failure	13 ± 4%
NRM (day +100)	10 ± 4%
Overall NRM	23 ± 5%

Immune reconstitution





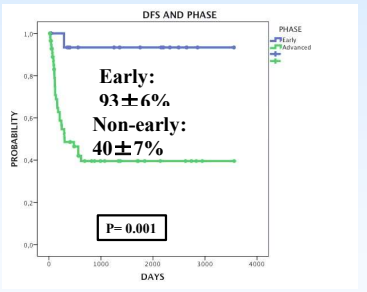


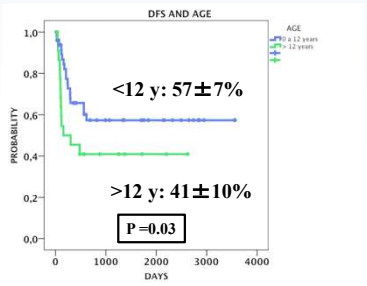
DFS multivariate analysis

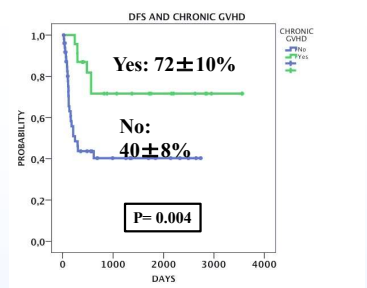
Variable	HR (CI 95%)	p
Chronic GVHD Yes	2.56 (0.99-6.63)	0.045
Age Child	2.18 (1.04-4.55)	0.04
Disease status Early	8.30 (1.09-62.7)	0.04
KIR haplotype B	2.59 (1.19-5.63)	0.01

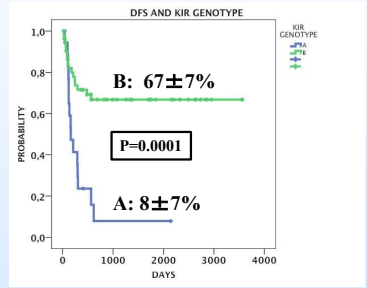
Conclusions

1) HAPLOIDENTICAL TRANSPLANTATION USING TCD IS ASSOCIATED WITH ENCOURAGING RESULTS ESPECIALLY IN PATIENTS IN EARLY PHASE OF DISEASE.
2) KIR B HAPLOTYPE DONORS CONFER A RAPID NK CELLS EXPANSION EARLY AFTER TRANSPLANTATION, RESULTING ON LOWER PROBABILITY OF RELAPSE AND SUGGESTING A GVL EFFECT APART FROM GVHD
3) HOWEVER, THE INCIDENCE OF SEVERE VIRAL INFECTIONS IS THE MAIN PROBLEM TO OVERCOME FOR REDUCING NRM (MAINLY IN ADOLESCENTS) AND IMPROVING RESULTS









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