Effect of graft source on safety and efficacy in patients undergoing hematopoietic stem cell transplantation

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INTRODUCTION

Donor availability remains a major challenge in allogeneic stem cell transplantations (HSCT). For patients who cannot find an HLA-matched sibling donor, current standard of care is a fully matched unrelated donor (MUD). However, not for all a MUD can be found and additional alternatives such as single loci mismatched unrelated donors, umbilical cord blood or haploidentical donors are used. Each alternative donor source and transplant regimen has its specific pro's and con's. In this retrospective study we collected transplant outcome data from different alternative donor transplants and compare these against the standard of care.

RESULTS

Characteristics	CD34-HAPLO	MUD	MMUD	UCB
Number of patients	35	64	37	22
Age (*yrs, median, range*)	43.0 (19-62)	47.5 (20-63)	54.0 (28-65)	38.5 (18-64)
Gender (% male)	57.1	53.1	37.8	54.5
Diagnosis (%)				
AML	71.4	67.2	67.6	63.6
ALL	11.4	14.1	18.9	22.7
MDS	17.1	18.8	13.5	13.6
Conditioning regimen (%)				
Myeloablative	74.4	53.1	56.8	59.1
RIC	25.7	46.9	43.2	40.9
TBI (%)				
None	28.6	4.7	59.5	0
Fractionated	54.3	32.8	21.6	54.5
Non-fractionated	17.1	12.5	18.9	45.5
Viable CD34+ (*x10^6 cells/kg, median, range*)	7 (2.18-15.1)	7 (1.5-920)	6.6 (0.63-390)	0.14 (0-13.7)
Viable CD3+ (*x10^4 cells/kg, median, range*)	3.95 (0.2-40)	9030 (1.47-50000)	4600 (0.71-39900)	911 (834-1200)
Neurophil engraftment (*days, median, range*)	16 (9-31)	17 (9-37)	17 (9-25)	20 (2-45)
Platelet engraftment (*days, median, range*)	23 (8-67)	18 (8-173)	16 (9-44)	39 (8-173)

Table 1. Patient characteristics per group.
Data on 158 subjects was collected: CD34-HAPLO =35; MUD=64; MMUD=37; UCB (double cord)=22.

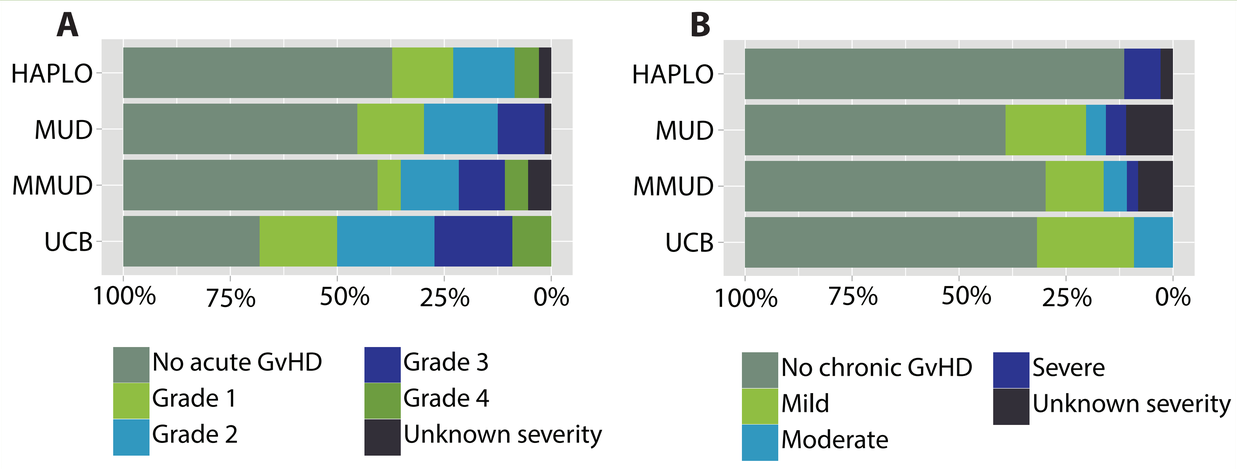

Figure 1. Maximum severity of GvHD event as percentage per group.
(A) Acute GvHD events as percentage per group. Acute GVDH grade III-IV was less frequent in the CD34-HAPLO group (6%) compared with other groups (MUD: 11%; MMUD: 16%; UCB: 27%).
(B) Chronic GvHD events as percentage per group. There was also less chronic GvHD in the CD34-HAPLO groups (11%) compared to the other groups (MUD: 39%; MMUD: 30%; UCB: 32%).

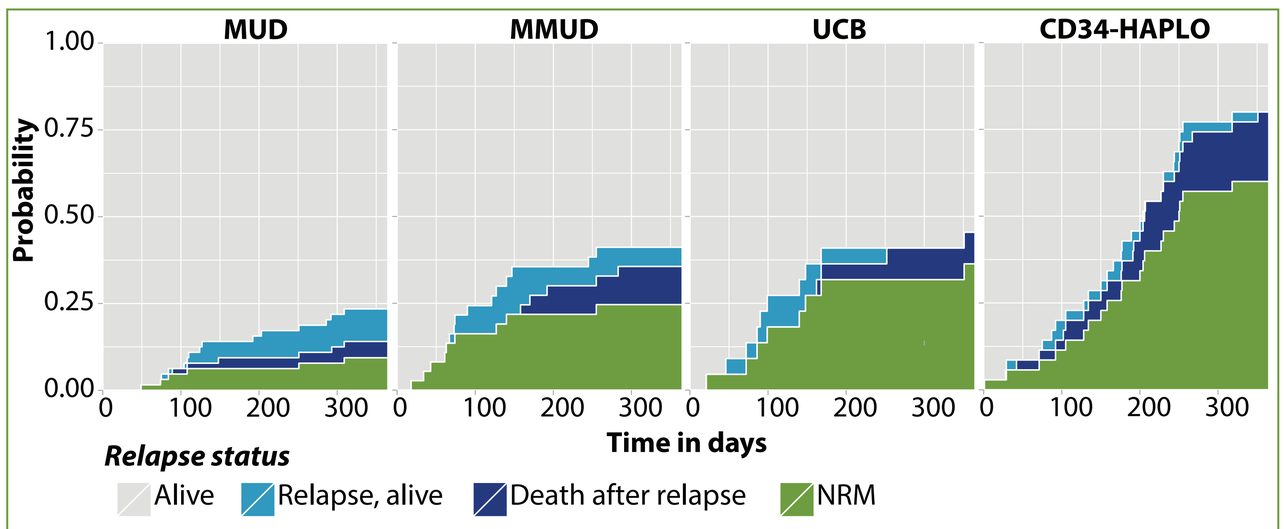

Figure 2. Stacked probabilities of relapse and death events per group.
Relapse occurred in 15% of the 158 patients with 12 months cumulative incidences of 20% in the CD34-HAPLO group, 14% in the MUD group, 16% in the MMUD group and 9% in the UCB group.

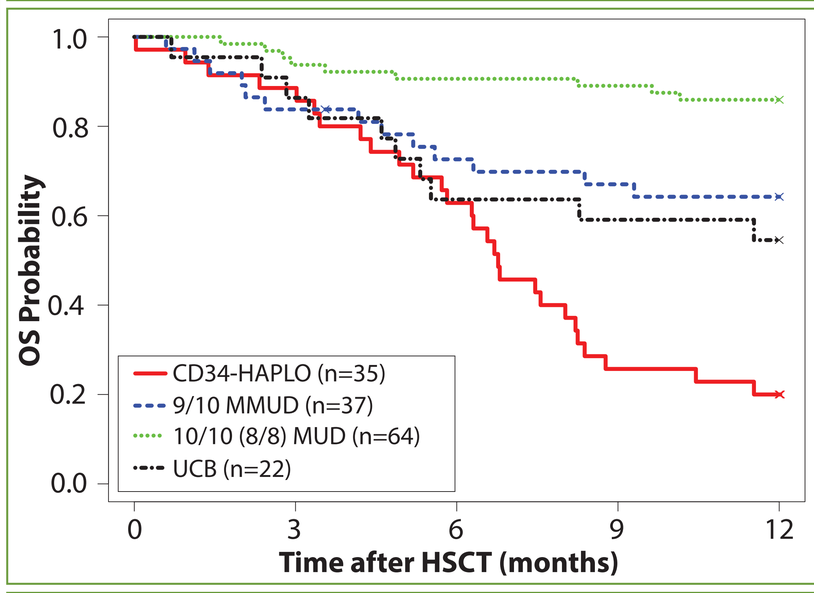

Figure 3. Overall Survival
Twelve month OS was lower for the CD34-HAPLO treatment group (20%) compared to all other treatment groups (MUD: 86%; MMUD: 64%; UCB: 55%).

NRM was lower for the MUD group (9%) compared to the other groups (CD34-HAPLO: 66%; MMUD: 25%; UCB: 36%).

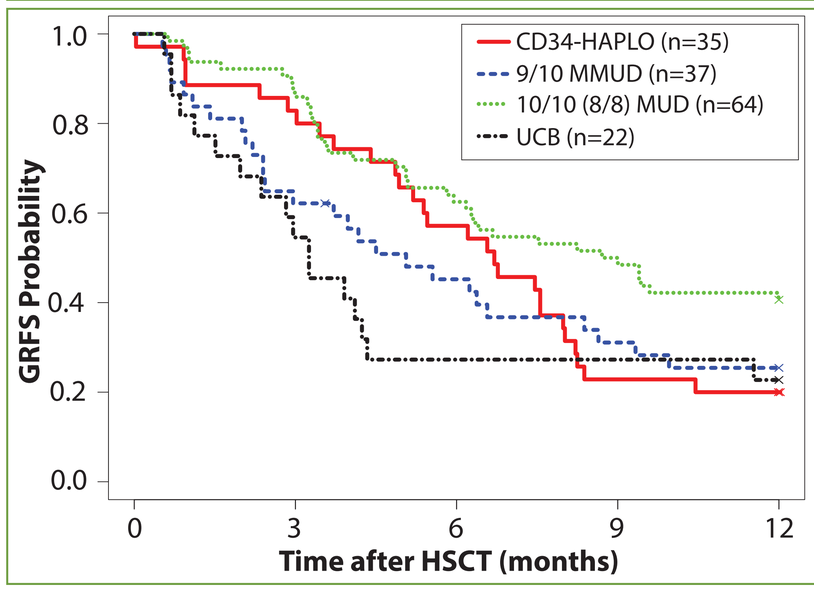

Figure 4.GvHD-Relapse Free Suvivial (GRFS)
GFRS is defined as alinve with no relapse, no grade III - IV acute GvHD and no chronic GvHD. This is a standard Kaplan-Meier analysis of survival.

When looking at the GRFS it is clear that MUD transplantations have the best outcome, and that all other alternative donor sources have a low GRFS at 1-year post-HSCT.

CONCLUSION

Our data show that the current alternatives (MMUD, UCB or CD34-HAPLO) have a worse outcome compared to standard of care (MUD). Use of MMUD or UCB donors shows higher rates of GVHD and NRM. Use of T-cell depleted haploidentical donors has substantially less GVHD, but more infections and thus much higher rates of NRM. On the GRFS endpoint all alternative donor sources perform poorly compared to MUD, as GVHD remains a major issue in MMUD and UCB transplants. In CD34-HAPLO NRM is the major drawback, as T-cell reconstitution is severely delayed. Adding additional donor lymphocytes post-HSCT could overcome limitation of this CD34+ selected HAPLO regimen. Data collected will serve as historic control group in the development of post-HSCT donor lymphocyte infusion, depleted of alloreactive T-cells (ATIR101).

MATERIALS & METHODS

In this retrospective, multicenter study (CR-AIR-006; NCT02188290) data was collected on outcome of HSCT in patients with AML or ALL (both in remission) or MDS, using either a fully matched (8/8 or 10/10) unrelated donor (MUD), a single-locus mismatched (9/10) unrelated donor (MMUD), umbilical cord blood (UCB) or a haploidentical (3/6, 4/6, 5/10, 6/10) donor (CD34-HAPLO). Transplantations were performed between January 2010 and January 2013 (MUD, MMUD, UCB) or between January 2006 and July 2013 (CD34-HAPLO). Haploidentical donor transplantations were conducted using myeloablative conditioning and a T-cell depleted (CD34$^+$ selection) graft. Non-relapse mortality (NRM) and overall survival (OS) up to 12 months post HSCT were compared between the four groups. In addition, incidence and severity of acute and chronic graft-versus-host disease (GvHD) up to 12 months was compared between groups. To determine clinical benefit of each transplantation regimen a composite end-point of GVHD-free, Relapse-Free Survival (GRFS) was used.

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Conflict of Interest statement

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