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Brief Article

Superior Graft-versus-Host Disease-Free Relapse-Free Survival in Matched Unrelated Donor Hematopoietic Stem Cell Transplantation with Anti-Thymocyte Globulin (ATG) Compared to Matched Related Donor without ATG

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The use of anti-T cell globulin (ATG) in allogeneic stem cell transplantation with matched unrelated donors (MUDs) is considered standard of care in many transplant centers, as these patients are at higher risk of developing acute and chronic graft-versus-host disease (GVHD). Several publications have reported reduced incidence of chronic GVHD compared to matched related donors (MRDs). This may support the idea of introducing ATG in prospective clinical trials, also in MRDs, in an effort to reduce the long-term complications with moderate and severe GVHD. We retrospectively analyzed 169 patients, in whom ATG was given to patients who underwent transplantation with MUDs (n = 124) and not MRDs (n = 45). The incidence acute GVHD II to IV and III to IV was significantly lower in the MUD group compared to the MRD group (28.2% versus 51.3% and 8.1% versus 24.7%). Extensive chronic GVHD incidence was 5% versus 40%. Our results further support the rationale for examining the efficacy of ATG in MRDs in prospective randomized trials.

For decades, an HLA-identical sibling donor has been the preferred choice of donor. Many studies have compared hematopoietic stem cell transplantation (HSCT) using matched unrelated donors (MUDs) and HLA-identical sibling donors and found results generally comparable [1]. MUDs have been associated with increased risk of acute and chronic graft-versus-host disease (GVHD). To reduce the risk of acute and chronic GVHD, several studies have shown that adding anti-T cell globulin, such anti-thymocyte globulin (ATG), reduces the incidence of chronic GVHD and increases GVHD-free relapse-free survival (GRFS). However, some studies have found a higher incidence of chronic GVHD when sibling donors were used, which is troublesome, as chronic GVHD in its most severe forms is potentially life-threatening and the factor most commonly associated with poor quality of life after HSCT [2]. Today, most European centers add ATG to the conditioning before HSCT when a MUD is used to reduce the risk for rejection and GVHD, whereas it is not as common in North American centers. Also, an increasing number of centers use post-transplant cyclophosphamide, especially in transplants with MUDs or haploidentical donors.

Recently, Othman et al. [3] published a study comparing the outcomes in 211 adult peripheral blood stem cell transplant recipients showing superior outcomes of HSCT when using a MUD with ATG compared to matched related donors (MRDs) without ATG. We have recently performed a retrospective analysis in our own registry in a comparable population with similar results.

METHODS

Patients were identified in the Oslo University Hospital Transplant Registry, where all allogeneic stem cell transplants are continuously registered. Patients with a diagnosis of acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), and myeloproliferative neoplasm (MPN)

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who underwent transplantation between January 2015 and February 2020 at Oslo University Hospital were chosen for statistical evaluation, comparing two HSCT strategies: (1) HLA-identical sibling donors without ATG versus (2) 10/10 HLA-matched MUDs including ATG. We used the same dose of thymoglobulin for all patients, 2 mg/kg/d for 2 days, with the last dose on day −1.

RESULTS

All patients received peripheral blood stem cells, reduced toxicity conditioning, and GVHD prophylaxis with cyclosporine and methotrexate. Most patients received fludarabin, 30 mg/m^2, for 4 to 5 days in combination with treosulfan (42 g/m^2) or busulfan (8 mg/kg). Characteristics of patients and donors are displayed in Table 1. In the MUD group, the donors were younger, the CD34$^+$ cell dose was higher, and an MDS diagnosis was more common.

Overall survival (OS) and GRFS was calculated using the Kaplan-Meier method and was compared using the log-rank test. Transplant-related mortality (TRM), GVHD, and relapse were estimated using cumulative incidence curves. Univariate and multivariate risk factor analyses were performed using the Cox regression. As the main purpose of the study was to compare the MUD + ATG and sibling donor without ATG groups, all analyses were corrected for differences between the 2 groups (donor age, diagnosis [AML, MDS, MPN], disease stage, CD34$^+$ cell dose, and sex mismatch [female donor to male patient]). Continuous variables were compared with the Mann-Whitney U test and categorical variables using the χ^2 method. Analyses were performed using the Statistica software (TIBCO, Palo Alto, CA, USA) and the EZR (http://www.jichi.ac.jp/saitama-sct/SaitamaHP.files/statmed.html) software.

Median follow-up for the whole cohort was 2 years (range, 0.5 to 5.6 years). OS, relapse, and TRM for the whole cohort were 55.3%, 28.5%, and 17.3%, respectively, with no difference between the MUD and sibling donor groups (Figure 1A). The

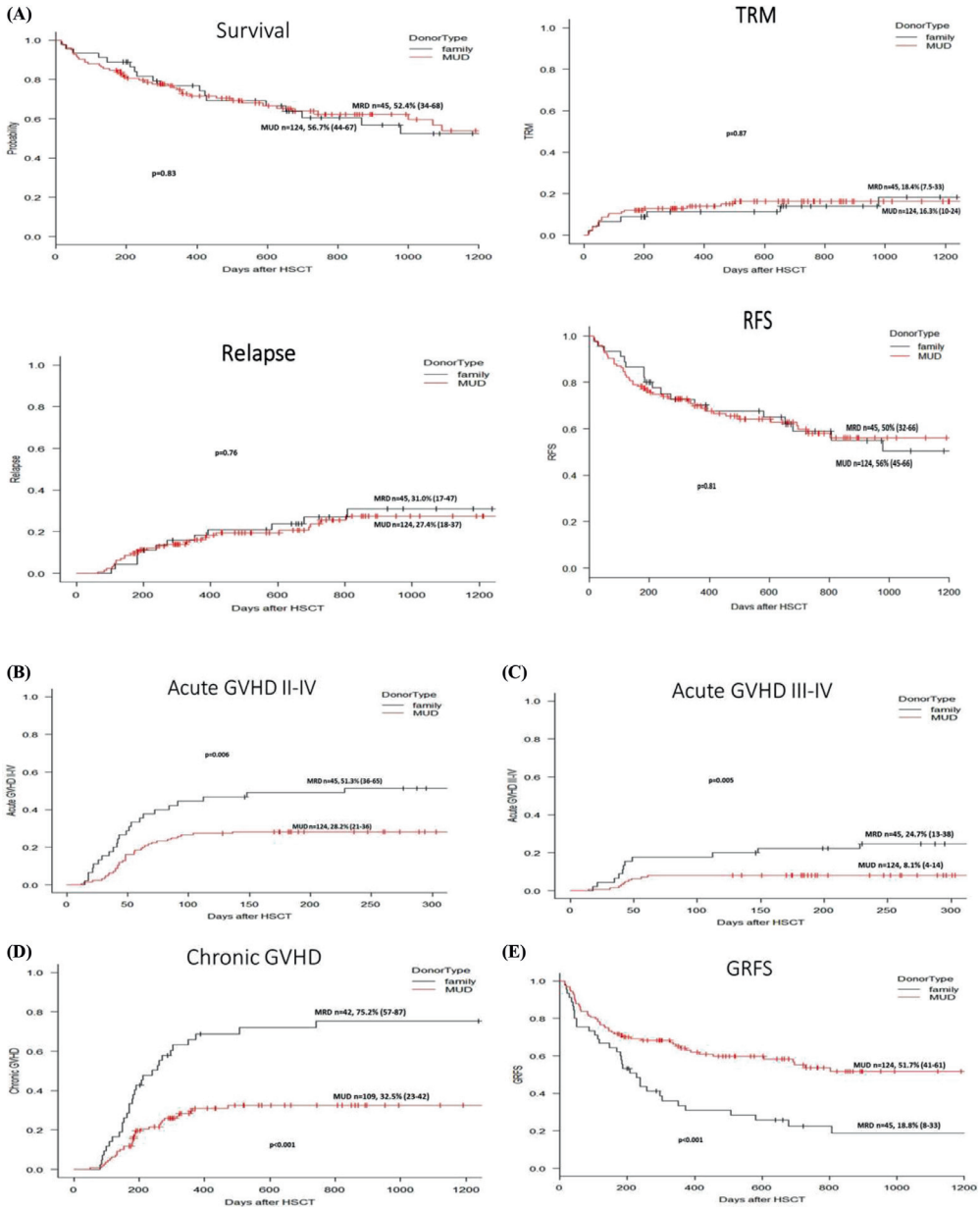

Figure 1. (A) Overall survival, (B) transplant-related mortality, (C) relapse, (D) relapse-free survival, (E) cumulative incidence of aGVHD II to IV, (F) aGVHD III to IV, (G) cGVHD, and (H) GRFS in patients with HLA-identical sibling donors or 10/10 HLA MUDs.

Table 1
Patient Characteristics

Factor	MRD	MUD + ATG	*P* Value
Number	45	124	
Age, years (median,range) (median	61 (30-72)	63 (18-72)	.15
Sex (M/F) (n,%)	33/12	88/36	.91
Diagnosis			.002
AML (n,%)	30 (67)	47 (38)	
MDS (n,%)	11 (24)	57 (46)	
MPN (n,%)	4 (9)	20 (16)	
Stage (early/late)(n,%)	23/22 (51/49)	45/79 (36/64)	.12
Donor age (median,range)	58 (33-74)	25 (18-55)	<.001
$CD34^+$ cell dose ($\times 10^6$/L) (median,range)	4.9 (2.3-7.0)	7.0 (3.0-20.2)	<.001
Female to male (n,%)	14 (31)	17 (14)	.01
Recipient CMV (−/+) (n,%)	13/32 (29/71)	33/91 (27/73)	.92
Donor CMV (−/+) (n,%)	16/29 (36/64)	65/59 (52/48)	.08
Follow-up, years (median, range)	2.4 (0.5-5.6)	1.8 (0.5-5.6)	.10

CMV indicates cytomegalovirus.

Table 2
Results from Multivariate Analyses of Factors Affecting Various Outcome Variables

Factor	HR	95% CI	*P* Value
Mortality			
MUD + ATG	1.01	0.46-2.22	.98
TRM			
MUD + ATG	0.65	0.19-2.38	.50
Relapse			
MUD + ATG	1.39	0.53-3.57	.51
CD34 dose <median	2.04	0.97-4.32	.06
RFS			
MUD + ATG	1.05	0.49-2.22	.90
Acute GVHD II-IV			
MUD + ATG	0.45	0.21-0.96	.04
Acute GVHD III-IV			
MUD + ATG	0.13	0.03-0.57	.007
MDS	5.10	1.15-22.5	.03
MPN	12.4	2.16-71.1	.005
AML	1.0	Reference	
Chronic GVHD			
MUD + ATG	0.15	0.06-0.34	<.001
CD34 dose <median	0.50	0.28-0.90	.02
Early stage	0.42	0.20-0.87	.02
GRFS			
MUD + ATG	0.41	0.21-0.81	.007
FtoM	1.86	1.10-3.13	.02

Only significant factors are shown.
HR indicates hazard ratio, RFS, relapse-free survival; FtoM, female donor to male recipient.

cumulative incidence of acute GVHD (aGVHD) grades II to IV and III to IV for all patients were 34.4% and 12.5%. We found lower incidences of both aGVHD II to IV (28.2% versus 51.3%, *P*= .006) and III to IV (8.1% versus 24.7%, *P* = .005) in the MUD group (Figure 1B,C). The cumulative incidence of chronic GVHD (cGVHD) for all patients was 45.4%, with a lower incidence (32.5% versus 75.2%, *P*< .001) in the MUD group (Figure 1D). Furthermore, the incidence of extensive cGVHD was lower in patients with an MUD compared to patients with a sibling donor, 5% versus 40%, $P < .001$. GRFS for all patients was 42.1%, with a significant superior GRFS in the MUD group (51.7% versus 18.8%, $P < .001$) (Figure 1E). In corrected multivariate analyses, we still found lower incidence of aGVHD II to IV (HR (hazard ratio), 0.45; 95% confidence interval [CI], 0.21 to 0.95; $P = .04$), III to IV (0.13; 95% CI, 0.03 to 0.57; $P < .01$), and cGVHD (0.14; 95% CI, 0.06 to 0.33; $P < .001$) and superior GRFS (0.41; 95% CI, 0.21 to 0.81; $P = .007$) in the MUD group compared to the sibling donor group (Table 2).

DISCUSSION

This retrospective study describes the outcome of 169 patients with a diagnosis of AML, MDS, or MPN who underwent transplantation between January 2015 and February 2020 at our institution. For all patients, an MRD was considered first choice, when available, and MUD as second choice.

All patients received reduced-intensity conditioning regimens, chosen on the basis of primary diagnosis, age, and comorbidities. Patients who underwent transplantation with MUDs received ATG as GVHD prophylaxis in addition to cyclosporine A and methotrexate.

Our results mirror the outcomes reported by Othman et al. [3] and show that sibling donor transplants seem to have similar OS, relapse-free survival, and TRM but higher incidences of aGVHD and cGVHD, resulting in inferior GRFS compared to MUD transplants when using the current protocols for conditioning and GVHD prophylaxis. In the study by Othman et al. [3], a few patients with a mismatched unrelated donor were included, which may have affected the result negatively for the MUD (matched unrelated donor) group. The dose of ATG differed minimally between our study and the study by Othman et al. [3], 4 mg/kg versus 4.5 mg/kg, which probably has no effect on the results. These data are in line with the results from the randomized trial published by Kröger et al. [4], showing improved GFRS with 30 mg/kg antilymphocyte globulin in myeloablative conditioning (MAC) transplants with HLA MRDs. This clearly indicates that validation of the efficacy of ATG in both Reduced intensity conditioning and MAC matched related donor transplants should be tested in a prospective randomized trial.

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REFERENCES

1. Yakoub-Agha I, Mesnil F, Kuentz M, et al. Allogeneic marrow stem-cell transplantation from human leukocyte antigen-identical siblings versus human leukocyte antigen-allelic-matched unrelated donors (10/10) in patients with standard-risk hematologic malignancy: a prospective study from the French Society of Bone Marrow Transplantation and Cell Therapy. *J Clin Oncol*. 2006;24(36):5695–5702.
2. Remberger M, Aram G, Sundin M, et al. High incidence of severe chronic GVHD after HSCT with sibling donors: a single center analysis. *Bone Marrow Transplant*. 2016;51(11):1518–1521.
3. Othman J, Greenwood M, Moore J, et al. Unrelated donor transplant recipients given thymoglobulin have superior GRFS when compared to matched related donor recipients undergoing transplantation without ATG. *BBMT*. 2020;26(10):1868–1875.
4. Kröger N, Solano C, Wolschke C, et al. Antilymphocyte globulin for prevention of chronic graft-versus-host disease. *N Engl J Med*. 2016;374(1):43–53.