ARTICLE

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The role of anti-thymocyte globulin in allogeneic stem cell transplantation (HSCT) from HLA-matched unrelated donors (MUD) for secondary AML in remission: a study from the ALWP /EBMT

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We compared outcomes, of 1609 patients with secondary acute myeloid leukemia (sAML) undergoing allogeneic transplantation (HSCT) in first complete remission (CR1) from matched unrelated donors (MUD) from 2010 to 2021, receiving or not receiving anti-thymocyte globulin (ATG) (ATG-1308, no ATG-301). Median age was 60.9 (range, 18.5–77.8) and 61.1 (range, 21.8–75.7) years, ($p = 0.3$). Graft versus host disease (GVHD) prophylaxis was cyclosporin-A with methotrexate (41%) or mycophenolate mofetil (38.2%), without significant differences between groups. Day 28, engraftment (ANC > 0.5×10^9/L) was 92.3% vs 95.3% ($p = 0.17$), respectively. On multivariate analysis, ATG was associated with lower incidence of grade II-IV and grade III-IV acute GVHD ($p = 0.002$ and $p = 0.015$), total and extensive chronic GVHD ($p = 0.008$ and $p < 0.0001$), and relapse incidence (RI) ($p = 0.039$), while non-relapse mortality (NRM) did not differ ($p = 0.51$). Overall survival (OS), and GVHD-free, relapse-free survival (GRFS) were significantly higher in the ATG vs no ATG group, HR = 0.76 (95% CI 0.61–0.95, $p = 0.014$) and HR = 0.68 (95% CI 0.57–0.8, $p < 0.0001$), with a tendency for better leukemia-free survival (LFS), HR = 0.82 (95% CI 0.67–1, $p = 0.051$). The main causes of death were the original disease, infection, and GVHD. In conclusion, ATG reduces GVHD and improves LFS, OS, and GRFS in sAML patients without increasing the RI, despite sAML being a high-risk disease.

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INTRODUCTION

Secondary acute myeloid leukemia (sAML) comprises a heterogeneous group of diseases evolving from a preexisting hematologic disorder, predominantly myelodysplastic syndrome (MDS) and myeloproliferative disorders (MPD) or as a complication of prior cytotoxic chemotherapy or radiation therapy [1–4]. Secondary AML has been associated with inferior outcomes compared to de novo AML due to the antecedent hematological disorder, older age, more aggressive biology of the leukemia with adverse cytogenetics and poor-risk mutation profile, lower susceptibility and lower ability to tolerate chemotherapy, and others [5–7]. Allogeneic hematopoietic cell transplantation (HSCT) remains the only known potentially curative therapy; however, results are still unsatisfactory [8–12]. Acute and chronic graft-versus-host disease (GVHD) is a major cause of non-relapse mortality (NRM) in HSCT from matched unrelated donors (MUD) for AML and theoretically even more so in sAML as patients are older and with more comorbidities, known risk factors for GVHD [8–11, 13, 14]. Acute GVHD is commonly observed in 40–60% of patients after MUD with overall survival (OS) of 10–25% in patients with severe grades III–IV GVHD, with some improvement in survival in recent years [13]. Historically, the standard backbone regimen for the prevention of GVHD after HSCT consists of a combination of a calcineurin inhibitor (CNI) and a short course of methotrexate (MTX) [15–17]. In MUD transplants, anti-thymocyte globulin (ATG) is incorporated into the anti-GVHD prophylaxis regimens in combination with a CNI and either MTX or mycophenolate mofetil (MMF)

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based on several randomized studies demonstrating a significant reduction in GVHD incidence with ATG (reviewed in [18–21]). Reduction of GVHD incidence post MUD transplantation is, therefore, a primary goal in HSCT for sAML aiming to reduce NRM and improve transplantation outcome, which is currently inferior in sAML in comparison to the outcomes of HSCT in de novo AML [11]. However, ATG as a broad and effective immunosuppression may increase the frequency of post-transplantation relapse of acute leukemia and especially of high-risk leukemia such as sAML. At least from a theoretical point of view ATG, may suppress the anti-leukemic attack of the donor immune cells in the graft against the recipient leukemic cells, the so-called graft-versus-leukemia (GVL) effect which is an essential component and the immunological basis of the HSCT curative potential in high-risk AML including sAML, especially as the GVL effect is usually in association with GVHD [22–25]. On the other hand, ATG has been shown to mediate a direct antitumor effect, mediating antibody-dependent cellular cytotoxicity (ADCC) in various hematological malignancies including acute leukemia [26–29]. In addition, higher post-HSCT natural killer (NK) -cell activity has been shown in patients receiving ATG as compared with patients receiving the anti-CD52 monoclonal antibody alemtuzumab [30]. Notably, most of the published studies that examined the interplay between GVL and GVHD looked at de novo rather than sAML [22–25]. We, therefore, wanted to assess the putative role of ATG in MUD transplantation, focusing on sAML and comparing transplantation outcomes in patients receiving ATG or not, in addition to CNI-based anti-GVHD prophylaxis. Such a comparison has not yet been performed for sAML.

PATIENTS AND METHODS

Study design and data collection

This was a retrospective, multicenter analysis using the dataset of the Acute Leukemia Working Party (ALWP) of the European Society for Blood and Marrow Transplantation (EBMT). The EBMT is a voluntary working group of more than 600 transplant centers that are required to report all consecutive stem cell transplantations and follow-ups once a year. EBMT minimum essential data forms are submitted to the registry by transplant center personnel following written informed consent from patients in accordance with the centers' ethical research guidelines. Data accuracy is assured by the individual transplant centers and by quality control measures such as regular internal and external audits. In addition, the study protocol was approved by each site and complied with country-specific regulatory requirements.

Eligibility criteria for this analysis included adult patients ≥18 years of age with sAML in first complete remission (CR1) who underwent a first HSCT from a 10/10 human leukocyte antigen (HLA) MUD with or without ATG as part of GVHD prophylaxis between 2010 and 2021. The exclusion criteria were HSCT from other donor types (sibling, haploidentical, or cord blood donor), previous history of HSCT, ex vivo T cell-depleted hematopoietic cell graft (all methods), and disease status >CR1 before transplantation. Data collected included recipient and donor characteristics (age, gender, cytomegalovirus (CMV)) serostatus, Karnofsky performance status (KPS) and hematopoietic cell transplantation specific comorbidity index (HCT-CI), disease characteristics, the antecedent diagnosis, year of transplant, type of conditioning regimen, stem cell source, and GVHD prophylaxis regimen. The conditioning regimen was defined as myeloablative (MAC) when containing total body irradiation (TBI) with a dose >6 Gray or a total dose of busulfan (Bu) > 8 mg/kg or >6.4 mg/kg when administered orally or intravenously, respectively. All other regimens were defined as reduced intensity conditioning (RIC) [31]. Grading of acute (a) GVHD was performed using established criteria [32]. Chronic (c) GVHD was classified as limited or extensive according to published criteria [33]. For this study, all necessary data were collected according to the EBMT guidelines, using the EBMT minimum essential data forms. The list of institutions contributing data to this study is provided in the Supplemental Appendix.

STATISTICAL ANALYSIS

The median, range, and interquartile range (IQR) were used to express quantitative variables and frequency and percentage for categorical variables. The study endpoints were OS, leukemia-free survival (LFS), relapse incidence (RI), NRM, engraftment, aGVHD, cGVHD, and GVHD-free, relapse-free survival (GRFS). All endpoints were measured from the time of transplantation. Engraftment was defined as achieving an absolute neutrophil count of 0.5×10^9/L for three consecutive days. OS was defined as time to death from any cause. LFS was defined as survival with no evidence of relapse or progression. NRM was defined as death from any cause without previous relapse or progression. We used modified GRFS criteria. GRFS events were defined as the first event among grade III-IV aGVHD, extensive cGVHD, relapse, or death from any other cause [34]. Patient, disease, and transplant-related characteristics for the two cohorts (ATG and no ATG) were compared using the Mann–Whitney *U* test for numerical variables, and the chi-squared or Fisher's exact test for categorical variables. The probabilities of OS, LFS, and GRFS were calculated using the Kaplan–Meier estimate. The RI and NRM were calculated using cumulative incidence functions in a competing risk setting, with death in remission being treated as a competing event for relapse. Early death was considered as a competing event for engraftment. To estimate the cumulative incidence of acute or cGVHD, relapse and death were considered as competing events. Univariate analyses were performed using the log-rank test for LFS and OS while Gray's test was used for cumulative incidence. Multivariate analyses (MVA) were performed using the Cox proportional-hazards regression model [35]. In order to take into account, the heterogeneity in the effect of a characteristic or a treatment across centers, we introduce a random effect (also named frailty effect) in Cox multivariate models. Then, the same random effect is shared by all patients within the same center [36]. Results were expressed as the hazard ratio (HR) with a 95% confidence interval (95% CI). All p values were two-sided with a type 1 error rate fixed at 0.05. Statistical analyses were performed with SPSS 25.0 (SPSS Inc., Chicago, IL, USA) and R 4.0.2 (R Core Team Fifty (2020). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/) [37, 38].

RESULTS

Patient, disease, and transplant-related characteristics

A total of 1609 patients met the inclusion criteria, 1308 received ATG as part of the pre-transplant preparative regimen, while 301 were conditioned without ATG. Table 1 shows the baseline demographic and clinical characteristics. Median follow-up was shorter for the ATG compared to the no ATG group being 41.6 (IQR, 37.3–46.3) and 60.2 (IQR, 53.2–73.4) months, respectively ($p = 0.001$). Median age was 60.9 (range, 18.5–77.8) and 61.1 (range, 21.8–75.7) years, respectively ($p = 0.3$). Patients in the ATG group were transplanted more recently, with a median year of transplant 2016 vs 2014 ($p < 0.0001$), and 51.5% and 53.2% of the patients with ATG and no ATG, were male ($p = 0.59$). In 75.8% and 75.6% of the ATG and no ATG patients with available information, respectively, the antecedent hematological disorder was myelodysplastic syndrome/myeloproliferative disorder (MDS/MPD), while in 13.2% and 14.1%, it was a solid tumor, other hematological diseases in 9.9% and 9%, aplasia or other nonmalignant hematological disorder in 1.1% and 1.3%, respectively. The antecedent disorder was unknown in 320 and 67 patients with or without ATG, respectively. All patients were transplanted in CR1. The two groups did not differ in cytogenetic risk, patient and donor CMV serostatus, and time from diagnosis to transplant. The cytogenetic risk was categorized as favorable (2.2% vs 3.5%), intermediate (68.0% vs 66.9%), or adverse (29.7% vs 29.6%) for patients with or without ATG, respectively ($p = 0.66$). The KPS was significantly lower in the ATG group in comparison with the no ATG group, with KPS < 90 in 31.9% versus 24.8%, respectively, $p = 0.021$. The HCT-CI was similar between the

Table 1. Patient, donor, and transplantation-related characteristics.

	Overall ($n = 1609$)	No ATG ($n = 301$)	ATG ($n = 1308$)	*P*
Follow-up (months), median [IQR]	46.1 [42.1–49.2]	60.2 [53.2–73.4]	41.6 [37.3–46.3]	0.001
Patient age, median (min-max) [IQR]	60.9 (18.5–77.8) [53.5–66.2]	61.1 (21.8–75.7) [53.2–67.4]	60.9 (18.5–77.8) [53.5–65.9]	0.3
Previous diagnosis				
MDS/MPN	926 (75.8%)	177 (75.6%)	749 (75.8%)	
Other hematological diseases	119 (9.7%)	21 (9%)	98 (9.9%)	
Solid tumors	163 (13.3%)	33 (14.1%)	130 (13.2%)	
Aplasia	5 (0.4%)	1 (0.4%)	4 (0.4%)	
Other non-malignant disorders	9 (0.7%)	2 (0.9%)	7 (0.7%)	
Unknown	387	67	320	
Year transplant, median (min-max)	2015 (2010-2021)	2014 (2010–2021)	2016 (2010–2021)	< 0.0001
Cytogenetics				
Favorable	24 (2.4%)	5 (3.5%)	19 (2.2%)	0.66
Intermediate	672 (67.9%)	95 (66.9%)	577 (68.0%)	
Adverse	294 (29.7%)	42 (29.6%)	252 (29.7%)	
NA/failed	619	159	460	
Time diagnosis to HSCT (mo), median (min-max) [IQR]	4.6 (1.1–17.6) [3.6–6.1]	4.7 (1.5–16.6) [3.6–6.2]	4.6 (1.1–17.6) [3.5–6.1]	0.48
Missing	2	1	1	
HCT-CI				
HCT-CI = 0	357 (36.1%)	62 (35.8%)	295 (36.2%)	1
HCT-CI = 1 or 2	172 (17.4%)	30 (17.3%)	142 (17.4%)	
HCT-CI > = 3	460 (46.5%)	81 (46.8%)	379 (46.4%)	
Missing	620	128	492	
Karnofsky performance status				
<90	461 (30.6%)	70 (24.8%)	391 (31.9%)	0.021
>=90	1048 (69.4%)	212 (75.2%)	836 (68.1%)	
Missing	100	19	81	
Patient sex				
Male	833 (51.8%)	160 (53.2%)	673 (51.5%)	0.59
Female	776 (48.2%)	141 (46.8%)	635 (48.5%)	
Donor sex				
Male	1176 (74.3%)	205 (69.3%)	971 (75.4%)	0.028
Female	407 (25.7%)	91 (30.7%)	316 (24.6%)	
Missing	26	5	21	
Female to male combination				
No F- > M	1457 (91.3%)	272 (91.3%)	1185 (91.4%)	0.96
F- > M	138 (8.7%)	26 (8.7%)	112 (8.6%)	
Missing	14	3	11	
Patient CMV				
Neg	580 (36.4%)	103 (34.9%)	477 (36.7%)	0.56
Pos	1014 (63.6%)	192 (65.1%)	822 (63.3%)	
Missing	15	6	9	
Donor CMV				
Neg	857 (53.9%)	153 (51.5%)	704 (54.4%)	0.36
Pos	733 (46.1%)	144 (48.5%)	589 (45.6%)	
Missing	19	4	15	
Cell source				
BM	104 (6.5%)	36 (12%)	68 (5.2%)	< 0.0001
PB	1505 (93.5%)	265 (88%)	1240 (94.8%)	

Table 1. continued

	Overall ($n = 1609$)	No ATG ($n = 301$)	ATG ($n = 1308$)	P
Conditioning				
MAC	579 (36%)	85 (28.2%)	494 (37.8%)	0.002
RIC	1028 (64%)	216 (71.8%)	812 (62.2%)	
Missing	2	0	2	
MRD at HSCT				
Neg	127 (54%)	15 (51.7%)	112 (54.4%)	0.79
Pos	108 (46%)	14 (48.3%)	94 (45.6%)	
Missing	1374	272	1102	

ATG anti-thymocyte globulin, *IQR* interquartile range, *min* minimum, *max* maximum, *MDS* myelodysplastic syndrome, *MPD* myeloproliferative disorder, *F* female, *M* male, *HCT-CI* hematopoietic cell transplantation-specific comorbidity index, *KPS* karnofsky performance status, *CMV* cytomegalovirus, *neg* negative, *pos* positive, *BM* bone marrow, *PB* peripheral blood, *MRD* measurable residual disease, *MAC* myeloablative conditioning, *RIC* reduced intensity conditioning, *HSCT* hematopoietic stem cell transplantation.

Table 2. Univariate analysis.

	2 years				
	Relapse	**NRM**	**LFS**	**OS**	**GRFS**
No ATG	33.5% [28–39.1]	17.9% [13.6–22.6]	48.6% [42.5–54.3]	54.4% [48.3–60.1]	30.6% [25.2–36.2]
ATG	25.4% [22.8–28]	21% [18.7–23.5]	53.6% [50.6–56.5]	59.3% [56.3–62.2]	45.1% [42.2–48.1]
P value	0.017	0.75	0.047	0.018	0.001
	180 days		**2 years**		
	Acute GVHD II-IV	**Acute GVHD III-IV**	**chronic GVHD**	**ext. chronic GVHD**	
No ATG	31.8% [26.5–37.2]	11% [7.7–14.9]	40.7% [34.7–46.6]	24.5% [19.5–29.9]	
ATG	24.9% [22.6–27.3]	8.1% [6.7–9.7]	32.9% [30–35.8]	13.4%[11.4–15.6]	
P value	0.009	0.08	0.027	0.001	

ATG anti -thymocyte globulin, *NRM* non-relapse mortality, *LFS* leukemia-free survival, *OS* overall survival, *GVHD* graft-versus-host disease, *GRFS-GVHD-free* relapse-free survival, *ext* extensive.

groups as was the median time from diagnosis to HSCT (Table 1). A higher number of patients in the ATG group received peripheral blood (PB) grafts (94.8% vs 88%, $p < 0.0001$) and MAC (37.8% vs 28.2%, $p = 0.002$) (Table 1). The most frequent conditioning regimen for the ATG group was Bu/fludarabine (Flu) at 43.6% and Flu/treosulfan at 18.5%, followed by Bu/Cytoxan (Cy) in 10.3% and Flu/melphalan (Mel) in 6.4% (Supplementary Table S1). The most frequent conditioning regimen for the no ATG group was Flu/low dose TBI in 46.3% and Bu/Flu in 19.7% followed by Bu/Cy in 10% and Flu/Mel in 6.7%, respectively (Supplementary Table S1). Anti-GVHD prophylaxis was cyclosporin-A with MTX (43% vs 32.2%) or with MMF (37.7% vs 40.5%), in patients conditioned with or without ATG, respectively (Supplementary Table S2).

Transplantation outcomes

Day 28 cumulative incidence of engraftment (ANC > 0.5×10^9/L) was 92.3% and 95.3% in the ATG and no ATG groups ($p = 0.17$), respectively (Supplementary Table S3). Day 180 incidence of aGVHD grades II-IV was significantly lower in the ATG vs no ATG patient groups 24.9% (range, 22.6–27.3%) vs. 31.8% (range, 26.5–37.2%) ($p = 0.009$), while severe grades III-IV aGVHD was observed in the ATG compared to the no ATG groups 8.1% (range, 6.7–9.7%) in the ATG group vs 11% (range,7.7–14.9%) in the no ATG group ($p = 0.08$) (Table 2). Two-year total and extensive chronic GVHD were lower in patients receiving ATG 32.9% (range, 30–35.8%) vs. 40.7% (range, 34.7–46.6%) ($p = 0.027$) and 13.4% (range, 11.4–15.6%) vs. 24.5% (range, 19.5–29.9%) ($p = 0.001$), respectively (Fig. 1, Table 2). ATG was associated with significantly better 2-year LFS, OS, and GRFS in the ATG compared to the no ATG groups with 53.6% (range, 50.6–56.5%) vs 48.6% (range, 42.5–54.3%) ($p = 0.047$); 59.3% (range, 56.3–62.2%) vs 54.4% (range, 48.3–60.1%) ($p = 0.018$) and 45.1% (range, 42.2–48.1%) vs 30.6% (range, 25.2–36.2%) ($p = 0.001$), respectively. RI was significantly lower in the ATG vs no ATG groups 25.4% (range, 22.8–28%) vs 33.5% (range, 28–39.1%) ($p = 0.017$), while 2-year NRM did not differ between the groups with 21% (range, 18.7–23.5%) vs 17.9% (range, 13.6–22.6%) ($p = 0.75$), for ATG vs no ATG, respectively (Table 2; Fig. 1).

Multivariate analysis

Patients in the ATG group were less likely to experience day 180-grade II-IV and grade III-IV aGVHD with HR = 0.62 (95% CI: 0.46–0.84), $p = 0.002$ and HR = 0.56 (95% CI: 0.35–0.89) $p = 0.015$, respectively. In addition, patients in the ATG group were less likely to experience total and extensive 2-year chronic GVHD HR = 0.7 (95% CI: 0.53–0.91), $p = 0.008$ and HR = 0.45 (95% CI: 0.3–0.66), $p < 0.0001$, respectively (Table 3). RI was also significantly lower in the ATG group compared to the no ATG group HR = 0.76 (95% CI: 0.59–0.99), $p = 0.039$. ATG was associated with significantly higher OS and GRFS and a numerically improved LFS compared to the no ATG group, HR = 0.76 (95% CI 0.61–0.95), $p = 0.014$, HR = 0.68 (95% CI 0.57–0.8), $p < 0.0001$, and HR = 0.82 (95% CI 0.67–1), $p = 0.051$, respectively. NRM did not differ between the two patient groups HR = 0.9 (95% CI 0.65–1.23), $p = 0.51$ (Table 3). Other significant prognostic factors in the MVA were adverse-risk cytogenetics which predicted a higher RI and inferior LFS, OS, GRFS, and lower total

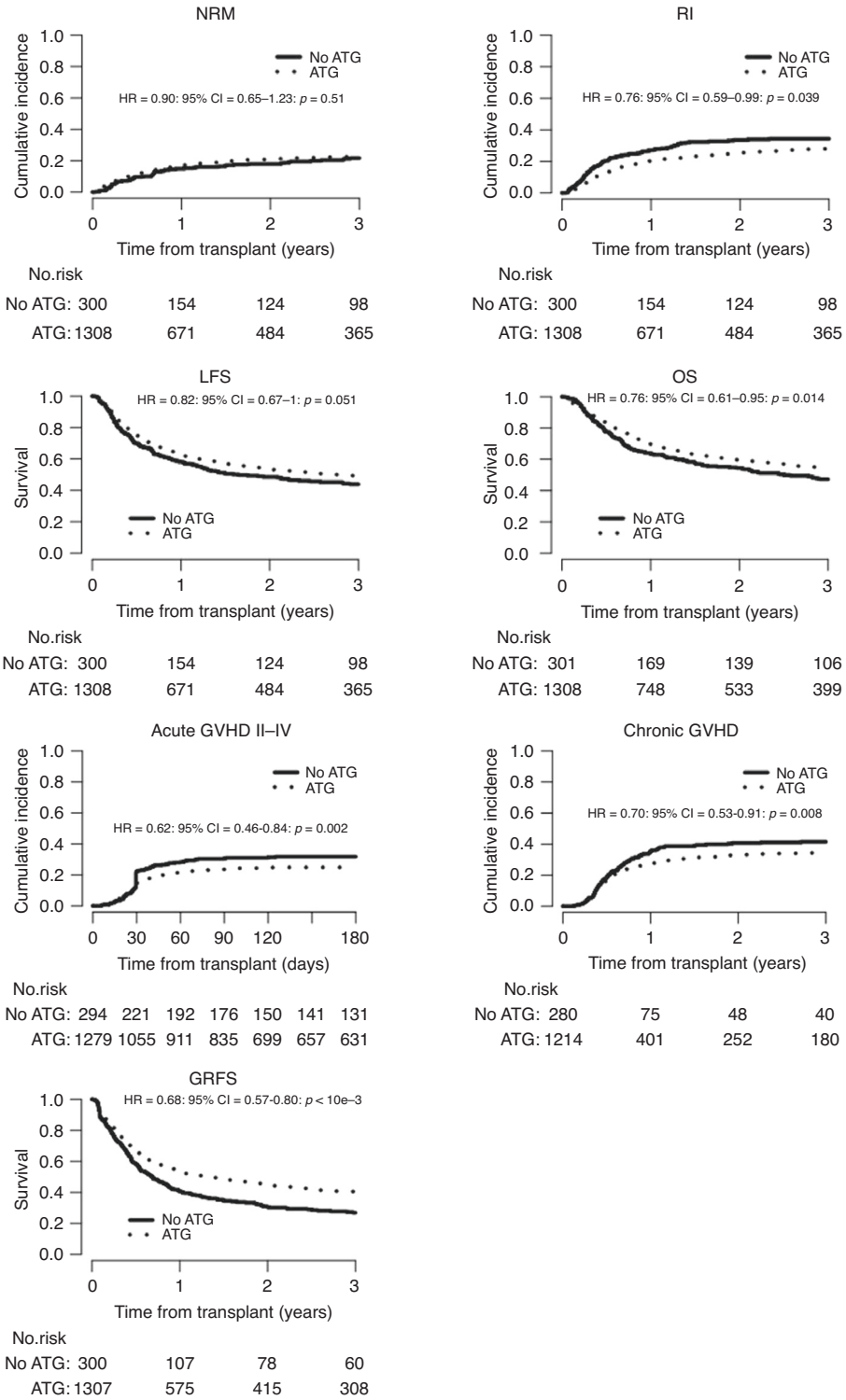

Fig. 1 Outcome of allogeneic stem cell transplantation (HSCT) from unrelated donors with or without anti-thymocyte globulin (ATG) in patients with secondary acute myeloid leukemia (sAML). Non-relapse mortality (NRM), relapse incidence (RI), leukemia-free survival (LFS), overall survival (OS), acute graft-versus-host disease (aGVHD), chronic GVHD, and GVHD-free, relapse-free survival (GRFS), hazard ratio (HR).

cGVHD; age (per 10 years) predicted a higher NRM and inferior LFS, OS, and GRFS. A KPS > 90 was a prognostic factor for lower NRM, and better LFS and OS. Patient CMV seropositivity was associated with a lower incidence of aGVHD (II-IV and III-IV). Finally, a recent year of transplant was associated with a lower NRM but a higher risk of extensive cGVHD (Table 3). The results basically remained the same when only patients with the known antecedent diagnosis were included in the MVA, with no difference between patients with sAML following MDS/MPN compared to others (Supplementary Table S4).

Cause of death

A total of 562 patients in the ATG group and 166 patients in the non-ATG group died during the study period (Table 4). Original disease was the main cause of death with 45.7% and 54.5% in

Table 3. Multivariate analysis.

	RELAPSE		NRM		LFS	
	HR (95% CI)	***P***	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
ATG vs No ATG	0.76 (0.59–0.99)	0.039	0.9 (0.65–1.23)	0.51	0.82 (0.67–1)	0.051
Patient age (per 10 years)	1.01 (0.91–1.12)	0.85	1.27 (1.12–1.44)	0.0003	1.11 (1.02–1.2)	0.01
Adverse cytogenetics	2.2 (1.75–2.76)	<0.0001	1.06 (0.78–1.44)	0.72	1.65 (1.38–1.98)	<0.0001
Time diagnosis to HSCT (mo)	0.98 (0.94–1.03)	0.43	0.99 (0.94–1.04)	0.6	0.99 (0.95–1.02)	0.37
KPS > 90	1.04 (0.83–1.31)	0.73	0.67 (0.52–0.85)	0.001	0.85 (0.72–1)	0.05
RIC vs MAC	1.19 (0.94–1.51)	0.15	1.02 (0.78–1.34)	0.87	1.11 (0.93–1.33)	0.23
Female to male vs other	0.95 (0.67–1.37)	0.8	0.9 (0.6–1.36)	0.61	0.94 (0.72–1.23)	0.64
Pat. CMV pos	0.92 (0.74–1.14)	0.45	1.19 (0.91–1.54)	0.2	1.03 (0.87–1.21)	0.77
Don. CMV pos	1.01 (0.82–1.25)	0.94	1.05 (0.83–1.34)	0.68	1.02 (0.87–1.2)	0.79
Year of HSCT	1.02 (0.99–1.06)	0.21	0.96 (0.92–1)	0.048	0.99 (0.97–1.02)	0.68
PBCS vs BM	0.85 (0.58–1.26)	0.42	1.24 (0.76–2.02)	0.4	0.99 (0.73–1.34)	0.95
	OS		**GRFS**		**Acute GVHD II-IV**	
	HR (95% CI)	***P***	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
ATG vs No ATG	0.76 (0.61–0.95)	0.014	0.68 (0.57–0.8)	<0.0001	0.62 (0.46–0.84)	0.002
Patient age (per 10 years)	1.14 (1.05–1.25)	0.002	1.09 (1.01–1.17)	0.018	1.02 (0.92–1.14)	0.69
Adverse cytogenetics	1.54 (1.27–1.87)	<0.0001	1.45 (1.23–1.71)	<0.0001	0.95 (0.72–1.25)	0.72
Time diagnosis to HSCT (mo)	0.99 (0.96–1.02)	0.54	0.98 (0.95–1.01)	0.22	0.99 (0.94–1.03)	0.53
KPS > 90	0.8 (0.67–0.95)	0.011	0.9 (0.78–1.05)	0.18	1.05 (0.83–1.34)	0.66
RIC vs MAC	1.15 (0.95–1.39)	0.17	1.06 (0.91–1.24)	0.44	1.04 (0.8–1.34)	0.79
Female to male vs other	0.96 (0.73–1.28)	0.8	1.06 (0.83–1.34)	0.65	1.27 (0.9–1.79)	0.17
Pat. CMV pos	1.02 (0.85–1.22)	0.83	0.96 (0.82–1.12)	0.6	0.7 (0.56–0.89)	0.003
Don. CMV pos	1.12 (0.95–1.33)	0.18	1.01 (0.88–1.17)	0.88	1.13 (0.9–1.42)	0.28
Year of HSCT	0.99 (0.97–1.02)	0.65	1.01 (0.99–1.04)	0.21	0.99 (0.96–1.02)	0.54
PBCS vs BM	1.01 (0.73–1.4)	0.93	0.93 (0.7–1.22)	0.6	0.92 (0.59–1.43)	0.71
	Acute GVHD III-IV		**chronic GVHD**		**extensive chronic GVHD**	
	HR (95% CI)	***P***	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
ATG vs No ATG	0.56 (0.35–0.89)	0.015	0.7 (0.53–0.91)	0.008	0.45 (0.3–0.66)	<0.0001
Patient age (per 10 years)	0.99 (0.82–1.18)	0.87	1.03 (0.94–1.13)	0.53	1.08 (0.94–1.25)	0.29
Adverse cytogenetics	1.03 (0.65–1.64)	0.89	0.68 (0.51–0.91)	0.01	0.75 (0.49–1.14)	0.18
Time diagnosis to HSCT (mo)	0.91 (0.83–1)	0.046	0.99 (0.95–1.03)	0.56	1 (0.93–1.06)	0.92
KPS > 90	0.91 (0.61–1.35)	0.63	1.05 (0.84–1.32)	0.64	1.09 (0.78–1.52)	0.62
RIC vs MAC	1.21 (0.79–1.87)	0.38	1.16 (0.92–1.45)	0.21	1.05 (0.75–1.47)	0.77
Female to male vs other	0.65 (0.3–1.4)	0.27	0.84 (0.58–1.2)	0.33	0.89 (0.54–1.47)	0.65
Pat. CMV pos	0.58 (0.39–0.87)	0.008	0.96 (0.77–1.19)	0.68	1.04 (0.76–1.43)	0.81
Don. CMV pos	1.3 (0.88–1.92)	0.19	0.9 (0.73–1.11)	0.31	1.02 (0.76–1.38)	0.89
Year of HSCT	0.99 (0.93–1.05)	0.74	1.01 (0.98–1.04)	0.57	1.07 (1.02–1.13)	0.008
PBSC vs BM	0.9 (0.42–1.92)	0.78	1.25 (0.81–1.92)	0.32	1.17 (0.62–2.21)	0.63

ATG anti-thymocyte globulin, *mo* months, *HSCT* hematopoietic stem cell transplantation, *LFS* leukemia-free survival, *OS* overall survival, *NRM* non-relapse mortality, *GVHD* graft-versus-host disease, *GRFS-GVHD-free* relapse-free survival, *KPS* karnofsky performance status, *RIC* reduced intensity conditioning, *MAC* myeloablative conditioning, *PBSC* mobilized peripheral blood stem cells, *BM* bone marrow, *CMV* cytomegalovirus, *Pat* patient, *Don* donor, *HR* hazard ratio, *CI* confidence interval.

each group, respectively. The second most frequent cause of death was infection 20.1% and 10.3% followed by GVHD at 16% vs 20.5%, respectively (Table 4). Other causes of death were infrequent and are depicted in Table 4.

DISCUSSION

In the current study focusing on a large group of 1609 patients with sAML transplanted from MUD while in CR1, we have demonstrated the beneficial effect of ATG in terms of reduced risk of both acute and chronic GVHD and improved LFS, OS, and GRFS. Although not surprising as ATG has been previously shown to reduce the incidence of GVHD post-transplantation for both acute myeloid and lymphatic leukemia (17–20), to our knowledge our study is the first to demonstrate a significant reduction in GVHD by ATG in sAML, a reduction that led to a significant improvement in transplantation outcomes including OS and GRFS. As patients with sAML are typically older and with more comorbidities, the ability to reduce GVHD and improve transplantation outcomes in these patients is of special importance.

Table 4. Cause of death.

	Overall ($n = 728$)	No ATG ($n = 166$)	ATG ($n = 562$)
Original disease	331 (47.7%)	85 (54.5%)	246 (45.7%)
Infection	124 (17.9%)	16 (10.3%)	108 (20.1%)
GVHD	118 (17%)	32 (20.5%)	86 (16%)
Non HSCT related	50 (7.2%)	9 (5.8%)	41 (7.6%)
Other transp related	26 (3.7%)	7 (4.5%)	19 (3.5%)
Second malignancy	22 (3.2%)	5 (3.2%)	17 (3.2%)
MOF	7 (1%)	0 (0%)	7 (1.3%)
Cardiac toxicity	5 (0.7%)	0 (0%)	5 (0.9%)
Hemorrhage	5 (0.7%)	2 (1.3%)	3 (0.6%)
CNS toxicity	2 (0.3%)	0 (0%)	2 (0.4%)
Failure/Rejection	1 (0.1%)	0 (0%)	1 (0.2%)
VOD	1 (0.1%)	0 (0%)	1 (0.2%)
IP	1 (0.1%)	0 (0%)	1 (0.2%)
Lymphoproliferative disorder	1 (0.1%)	0 (0%)	1 (0.2%)
Missing	34	10	24

ATG anti-thymocyte globulin, *HSCT* hematopoietic stem cell transplantation, *GVHD* graft-versus-host disease, *MOF* multiorgan failure, *transp* transplantation, *CNS* central nervous system, *VOD* veno occlusive disease of the liver, *IP* interstitial pneumonitis.

Notably, the incidence of both acute and cGVHD was reduced by ATG despite the fact that a higher percentage of patients in the ATG compared to the no ATG group received mobilized PB stem cell grafts and MAC as the preparative regimen, both were previously shown to be associated with an increased risk of GVHD [39, 40]. The improvement in OS is of special interest as in many of the previous studies including the randomized studies of ATG vs no ATG in MUD for patients with de novo AML, the reduction in GVHD by ATG was not translated into improved OS [18, 41–43]. The currently observed improvement in OS and GRFS with the administration of ATG in MUD for sAML needs of course to be confirmed in a well-designed randomized study focusing on sAML. The fact that the reduced incidence of GVHD did not translate into a reduced risk of NRM may be due to an increased risk of other transplant-related complications including infections, in agreement with our previous publication [44]. In our current study, infections were the cause of death in 20.1% of the cases in the ATG group but only 10.3% in the non-ATG group.

Besides infections, the other theoretical concern about using ATG in the setting of allogeneic transplantation has always been the fear of an increase in the relapse rate of the original malignancy due to the heavy immunosuppressive effect of ATG. Furthermore, ATG eliminates alloreactive donor T cells [18, 45] and can therefore potentially reduce the GVL effect increasing the relapse rate, especially in high-risk leukemia [43, 46, 47]. We previously addressed this concern in high-risk AML including those harboring the FLT3+ mutation and with adverse-risk cytogenetics that underwent allogeneic transplantation with RIC, as well as AML patients with positive measurable residual disease pre-transplantation and observed no increase in leukemic relapse with ATG [48, 49]. We now show that adding ATG to the pre-MUD transplantation preparative regimens in high-risk leukemia such as sAML, results in a decreased relapse rate. This is to some extent, an unexpected result that needs to be confirmed in a randomized study; it may be explained by the direct antitumor effect observed with ATG in various hematological malignancies including acute leukemia [26–29]. In any event, the fact that ATG did not result in increased relapse rates in sAML patients undergoing unrelated donor transplantation is in agreement with our previous publications [48, 49] and is of major clinical importance. The other prognostic factors we observed in the MVA including cytogenetic risk, age, KPS, CMV serostatus, and year of transplant, are in agreement with previous publications of allogeneic transplantations including in sAML [9, 11, 12, 50–54]. Being retrospective and registry-based, this transplantation study has several limitations including a risk of selection bias and the possibility of unavailable data that could not have been considered, such as frontline therapies, molecular and MRD data, and doses and brands of ATG. We only included patients in CR1 who thus have more favorable outcomes, and results may differ with patients in more advanced stages of sAML. In addition, extended follow-up and specifically, quality-of-life measures, together with other patient-reported outcomes will be important endpoints to analyze in future studies. As other strategies for GVHD prophylaxis (posttransplant cyclophosphamide) are being developed, the role of ATG in GVHD prevention in sAML will need to be prospectively validated.

In summary, the incorporation of ATG-based anti-GVHD prophylaxis in MUD transplants for sAML resulted in lower GVHD rates and improved LFS, OS, and GRFS without increasing the disease relapse rate. Although this is a registry-based observational study, it is the largest analysis of its kind in patients with sAML and it demands a prospective validation of the role of ATG in unrelated donor transplants for sAML. Our findings offer an encouraging clinical message for this high-risk devastating acute leukemia.

DATA AVAILABILITY

AN, ML, and MM had full access to all study data (available upon data-specific request).

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AUTHOR CONTRIBUTIONS

AN wrote the manuscript, designed the study, and interpreted the data. ML and MM designed the study, performed the statistical analyses, interpreted the data, and edited the manuscript. NK, TS, TGD, ME, UP, IWB, US, RPDL, JS, MS, BS, and FC reviewed the manuscript and provided clinical data. All authors approved the final version of the manuscript.

COMPETING INTERESTS

The authors declare that they have no relevant conflict of interest and no competing financial interests. NK received a research grant and honorarium from Neovii.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The scientific boards of the ALWP of the EBMT approved this study.

ADDITIONAL INFORMATION

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