European Journal of Cancer 106 (2019) 212–219

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Impact of anti-thymocyte globulin on results of allogeneic peripheral blood stem cell transplantation for patients with Philadelphia-positive acute lymphoblastic leukaemia: An analysis by the Acute Leukemia Working Party of the EBMT

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Received 13 August 2018; received in revised form 20 October 2018; accepted 5 November 2018
Available online 6 December 2018

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https://doi.org/10.1016/j.ejca.2018.11.003

KEYWORDS
Acute lymphoblastic leukaemia;
Philadelphia positive;
Anti-thymocyte globulin;
Allogeneic haematopoietic cell transplantation;
Graft-versus-host disease;
Leukaemia-free survival

Abstract ***Background:*** Anti-thymocyte globulin (ATG) is widely used to prevent graft-versus-host disease (GVHD) after allogeneic peripheral blood stem cell transplantation (alloPBSCT). The goal of this study was to retrospectively assess the effect of ATG on outcomes in the setting of Philadelphia chromosome-positive acute lymphoblastic leukaemia (Ph+ ALL).

Methods: In the analysis, 1170 adult patients undergoing alloPBSCT from human leucocyte antigen–matched sibling or unrelated donors in the first complete remission between 2007 and 2016 were included. ATG was used in 429/575 (75%) and 121/595 (20%) patients transplanted from unrelated or sibling donors, respectively.

Results: The incidence of chronic GVHD was 35% for patients treated with ATG compared with 52% in those not receiving ATG ($p < 0.001$), while the rate of extensive chronic GVHD was 16% and 36%, respectively ($p < 0.001$). The probability of survival free from GVHD and relapse (GRFS) was 42% and 32%, respectively ($p = 0.002$). In a multivariate model, the use of ATG was associated with reduced risk of overall chronic GVHD (hazard ratio [HR] = 0.52, $p < 0.001$) and extensive chronic GVHD (HR = 0.46, $p < 0.001$). It was also associated with better GRFS (HR = 0.77, $p = 0.007$), despite increased risk of relapse (HR = 1.41, $p = 0.02$). No significant effect was found with regard to the risk of non-relapse mortality and overall mortality.

Conclusions: The use of ATG for patients with Ph+ ALL undergoing alloPBSCT is associated with reduced risk of chronic GVHD without impact on survival and therefore, could be considered. However, increased risk of relapse suggests the need for strict monitoring of minimal residual diseases and appropriate interventions after transplantation.

1. Introduction

The prognosis of patients with Philadelphia chromosome–positive acute lymphoblastic leukaemia (Ph+ ALL) improved markedly with the introduction of tyrosine kinase inhibitors (TKIs) [1,2]. However, without allogeneic haematopoietic stem cell transplantation (alloHSCT), most of the patients relapse, and therefore, transplantation from either human leucocyte antigen (HLA)–matched sibling (MSD) or unrelated donor (MUD) is still considered a standard of care [3–6]. Unfortunately, despite improvement over time, the procedure is still associated with significant mortality and morbidity [7]. Some complications, including chronic graft-versus-host disease (cGVHD), may negatively affect long-term quality of life [8]. Results of several randomised trials indicate an increased risk of cGVHD for transplantations using peripheral blood stem cell transplantation (PBSCT) compared with bone marrow, which is important in view of increasing proportion of PBSCTs among alloHSCT procedures [9,10].

Attempts to decrease the risk of cGVHD include *in vivo* T-cell depletion using anti-thymocyte globulin (ATG) as a part of a conditioning regimen [11]. Several prospective, randomised studies documented its efficacy with regard to both overall and extensive cGVHD after transplantation from either MUD or MSD [12–16]. Although the use of ATG may be associated with delayed immune reconstitution, most studies did not report its detrimental effect on the risk of relapse or the overall mortality. It must be stressed, however, that those studies included mainly patients with myeloid malignancies. While the effect of ATG on the risk of GVHD seems independent of the baseline diagnosis, theoretically, there may be differences regarding its impact on relapse. In this regard, for malignancies such as ALL in which a strong association between cGVHD and relapse incidence has been demonstrated, suppression of cGVHD may result in increased risk of disease recurrence [17,18]. The goal of the current analysis was to evaluate the impact of *in vivo* T-cell depletion using ATG on outcomes of patients with Ph+ ALL, treated with alloPBSCT. This population has been poorly represented in the recent prospective clinical trials, and therefore, no disease-specific conclusions are available so far.

2. Methods

2.1. Study design and data collection

This was a retrospective, multicentre analysis. Data were provided by the registry of the Acute Leukemia Working Party (ALWP) of the European Society For Blood and Marrow Transplantation (EBMT), representing more than 600 transplant centres that are required to report all consecutive stem cell transplantations and follow-ups. The quality control programme includes verification of the computer printout of the entered

data, cross-checking with the national registries, and on-site visits of selected teams. The study was approved by the ALWP of the EBMT institutional review board and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

2.2. Criteria of selection

The inclusion criteria were set as follows: (1) patients with Ph+ ALL who underwent their first alloHSCT in the first complete remission (CR1) between January 2007 and December 2016; (2) age $\geq$ 18 years; (3) transplantation from either MSD or MUD (8/8 HLA loci) and (4) the use of PBSC. Transplantations with *in vivo* T-cell depletion using agents other than ATG or those with *ex vivo* T-cell depletion were excluded from the analysis. Patients treated with post-transplant cyclophosphamide for GVHD prevention were also excluded.

2.3. Statistical analysis

Survival free from grade III-IV acute GVHD (aGVHD), cGVHD and relapse (GRFS) was the primary, composite study end-point. Secondary end-points were the following: (1) the incidence of grade II-IV and III-IV aGVHD; (2) the incidence of overall and extensive cGVHD; (3) non-relapse mortality (NRM); (4) relapse incidence (RI); (5) the probability of leukaemia-free survival (LFS) and (6) overall survival (OS). Patients' characteristics were compared using Kruskal–Wallis test for numerical variables and chi-square test for categorical variables. Cumulative incidence curves were used to estimate the probabilities of aGVHD, cGVHD, RI and NRM in a competing risk setting [19]. Probabilities of OS and LFS were calculated using the Kaplan–Meier estimates [20]. Univariate analyses were performed using log-rank test for LFS and OS and Gray's test for cumulative incidence. Multivariate analyses were performed using Cox proportional hazard model, including the following factors: patient age, year of alloHSCT, donor type (MUD or MSD), time from diagnosis to alloHSCT, patient and donor sex, patient and donor cytomegalovirus (CMV) serological status, conditioning intensity (reduced or myeloablative) and type of conditioning (irradiation or chemotherapy based) [21]. Proportional hazard assumptions were checked systematically for all proposed models using the Grambsch-Therneau residual-based test. All interactions between ATG and other covariates were checked. The median follow-up was 35 months. All tests were two sided with type I error rate fixed at 0.05. Statistical analyses were performed with SPSS 24.0 (IBM Corp., Armonk, NY, USA) and R 3.4.1 (R Core Team (2017). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/.)

3. Results

3.1. Patients, donors, and alloHSCT procedure

The analysis included 1170 adults, of whom 550 received ATG as *in vivo* T-cell depletion. ATG was used in 429/575 (75%) and 121/595 (20%) patients transplanted with PBSC from MUD or MSD, respectively. Conditioning regimen was myeloablative in 873 (75%) of the transplantations. The most frequently used immunosuppression protocol consisted of cyclosporin in combination with methotrexate (59%). Patients in the ATG group were significantly older, had longer interval from diagnosis to HSCT and were more frequently pretreated with TKIs but less frequently transplanted in molecular CR (Table 1). They were also more frequently given transplantation from MUD and from female donors to male recipients, had more frequently donors with negative CMV serological status and were less frequently treated with myeloablative conditioning.

Table 1
Patient characteristics.

Characteristics	ATG	No ATG	*P*
N	550	620	
Median patient age, years (range)	48 (18–76)	43 (18–72)	<0.001
Patient gender			
Female	265 (48%)	278 (45%)	0.25
Male	285 (52%)	342 (55%)	
Median interval from diagnosis to transplantation, months (range)	6 (2–23)	5 (1–24)	<0.001
Pretransplant use of TKIs			
Yes	230 (91%)	218 (82%)	<0.001
No	24 (9%)	47 (18%)	
Missing	296	355	
Disease status at transplantation			
Molecular remission	266 (57%)	312 (64%)	0.03
No molecular remission	200 (43%)	175 (36%)	
Missing	84	133	
Donor type			
HLA-matched sibling	121 (22%)	474 (76%)	<0.001
HLA-matched (8/8) unrelated	429 (78%)	146 (24%)	
Female donor to male recipient			
Yes	77 (14%)	126 (20%)	0.004
No	469 (86%)	490 (80%)	
Missing	4	4	
Donor/recipient CMV serostatus			
Negative/negative	137 (26%)	126 (22%)	<0.001
Positive/negative	56 (11%)	53 (9%)	
Negative/positive	161 (30%)	81 (14%)	
Positive/positive	177 (33%)	326 (56%)	
Missing			
Conditioning[a]			
Myeloablative, CHT based	117 (21%)	125 (20%)	<0.001
Myeloablative, TBI based	261 (48%)	370 (60%)	
Reduced intensity, CHT based	158 (29%)	65 (10%)	
Reduced intensity, TBI based	14 (3%)	60 (10%)	

ATG, anti-thymocyte globulin; TKIs, tyrosine kinase inhibitors; HLA, human leucocyte antigen; CMV, cytomegalovirus; CHT, chemotherapy; TBI, total body irradiation.

[a] The definition of myeloablative and reduced intensity conditioning was according to the published EBMT criteria [33].

3.2. Engraftment and GVHD

The engraftment rate was 97% and 98% for patients treated with or without ATG, respectively ($p = 0.28$). Time to neutrophil recovery $>0.5 \times 10^9$/L was delayed in the ATG group: 16 (2–78) days versus 15 (2–74) days, respectively ($p < 0.001$).

In a univariate analysis, the use of ATG was associated with decreased incidence of both overall and extensive cGVHD, while no effect on aGVHD could be demonstrated (Table 2). In a multivariate model, the use of ATG was shown to reduce the risk of grade III-IV aGVHD (hazard ratio [HR] = 0.67, $p = 0.049$), overall cGVHD (HR = 0.52, $p < 0.004$) and extensive cGVHD (HR = 0.46, $p < 0.004$) (Table 3, Fig. 1). In subgroup analysis stratified by the donor type, the effect the use of ATG on the overall cGVHD was similar for recipients of MSD-PBSCT (HR = 0.51, $p = 0.003$) and MUD-PBSCT (HR = 0.57, $p = 0.0003$). The impact on extensive cGVHD was significant only for patients treated with MUD-HSCT (HR = 0.4, $p < 0.0001$).

Among other risk factors, transplantations from MUD compared with MSD were associated with increased risk of grade II-IV and grade III-IV aGVHD as well as overall and extensive cGVHD. In addition, the risk of overall cGVHD was increased for patients treated with transplantation from donors with the CMV-positive serological status and in case of conditioning based on total body irradiation (TBI) (Table 3).

3.3. Non-relapse mortality

ATG was not found to affect NRM neither in univariate nor in multivariate analysis (Tables 2 and 3, Fig. 2). In the Cox model, only increasing recipient age was associated with increased risk of NRM (Table 3).

The most frequent causes of NRM in the ATG group were infections (38%), followed by GVHD (32%), veno-occlusive disease (6%) and interstitial pneumonitis (6%), while among patients not treated with ATG, predominant causes of NRM were GVHD (43%), infections (36%), veno-occlusive disease (4%) and secondary malignancies (3%).

3.4. Leukaemia relapse

In a univariate analysis, the incidence of relapse was comparable for patients in the ATG and 'no ATG' group. However, after adjustment to other potential prognostic factors, the use of ATG was associated with increased risk of relapse (HR = 1.41, $p = 0.02$) (Table 3, Fig. 2). The HRs were similar for recipients of MSD-HSCT (1.44) and MUD-HSCT (1.41), although the associations did not reach statistical significance ($p = 0.07$ and $p = 0.18$, respectively).

In the multivariate model, the following factors were associated with reduced risk of relapse: increasing year of transplantation, the use of MUD and the use of TBI-based conditioning (Table 3).

3.5. Survival

No significant impact of the use of ATG on LFS and OS could be observed in both univariate and multivariate analysis (Tables 2 and 3, Fig. 3). In the Cox model, the following factors were associated with reduced risk of treatment failure (either relapse or NRM and reverse LFS): increasing year of transplantation, the use of MUD and the use of TBI-based conditioning. Increasing year of transplantation and the use of TBI were also associated with reduced risk of the overall mortality, while increasing recipient age negatively affected survival (Table 3).

3.6. Survival free from relapse, aGVHD grade III–IV and cGVHD

In a univariate analysis, the use of ATG was associated with increased probability of GRFS (Table 2). The favourable effect of ATG on GRFS was confirmed in a multivariate model (HR = 0.77, $p = 0.007$) (Table 3, Fig. 4). No other factors were found to influence GRFS.

4. Discussion

In this retrospective analysis including a large homogenous group of 1170 individuals with Ph+ ALL treated

Table 2
Impact of ATG on the outcomes—results of univariate analysis.

Factor	RI at 2 years	NRM at 2 years	LFS at 2 years	OS at 2 years	GRFS at 2 years	aGVHD II-IV at 100 days	aGVHD III-IV at 100 days	Overall cGVHD at 2 years	Extensive cGVHD at 2 years
No ATG (N = 550)	27% (23–31)	20% (17–23)	53% (49–58)	67% (63–71)	32% (28–36)	34% (31–38)	15% (12–18)	52% (47–56)	26% (22–30)
ATG (N = 620)	26% (22–30)	21% (17–25)	53% (49–58)	67% (62–71)	42% (37–46)	36% (32–40)	12% (9–15)	35% (30–39)	16% (13–19)
P	0.94	0.92	0.95	0.9	0.002	0.55	0.2	<0.0001	<0.0001

ATG, anti-thymocyte globulin; RI, relapse incidence; CI, confidence interval; NRM, non-relapse mortality; LFS, leukaemia-free survival; OS, overall survival; GRFS, survival free from relapse, acute graft-versus-host disease grade III-IV and chronic graft-versus-host disease; aGVHD, acute graft-versus-host disease; cGVHD, chronic graft-versus-host disease.
Data on survival are presented as Kaplan–Meier estimates at 5 years (95% confidence interval).

Table 3
Multivariate analysis of factors associated with outcomes.

End-point	Factor	HR (95% CI)	*P*
RI	ATG vs. no ATG	1.41 (1.05–1.89)	0.02
	Year of transplantation	0.95 (0.9–0.99)	0.02
	MUD vs. MSD	0.48 (0.35–0.64)	<0.0001
	Conditioning: TBI based vs. CHT based	0.66 (0.5–0.88)	0.004
NRM	ATG vs. no ATG	0.84 (0.61–1.16)	0.29
	Age (per 10 years)	1.18 (1.04–1.33)	0.008
LFS	ATG vs. no ATG	1.11 (0.89–1.38)	0.34
	Year of transplantation	0.95 (0.92–0.99)	0.006
	MUD vs. MSD	0.77 (0.62–0.96)	0.02
	Conditioning: TBI based vs. CHT based	0.78 (0.63–0.96)	0.02
OS	ATG vs. no ATG	0.94 (0.73–1.2)	0.62
	Age (per 10 years)	1.12 (1.2–1.23)	0.01
	Year of transplantation	0.95 (0.91–0.99)	0.02
	Conditioning: TBI based vs. CHT based	0.74 (0.58–0.95)	0.02
GRFS	ATG vs. no ATG	0.77 (0.64–0.93)	0.007
aGVHD grade II-IV	ATG vs. no ATG	0.82 (0.64–1.05)	0.11
	MUD vs. MSD	2 (1.54–2.6)	<0.0001
aGVHD grade III-IV	ATG vs. no ATG	0.67 (0.45–1)	0.049
	MUD vs. MSD	1.61 (1.08–2.42)	0.02
Overall cGVHD	ATG vs. no ATG	0.52 (0.41–2.42)	<0.0001
	MUD vs. MSD	1.45 (1.15–1.84)	0.002
	Donor CMV serostatus: (+) vs. (−)	1.35 (1.08–1.68)	0.007
	Conditioning: TBI based vs. CHT based	1.28 (1–1.62)	0.046
Extensive cGVHD	ATG vs. no ATG	0.46 (0.33–0.64)	<0.0001
	MUD vs. MSD	1.56 (1.11–2.18)	0.009

CI, confidence interval; RI, relapse incidence; NRM, non-relapse mortality; LFS, leukaemia-free survival; OS, overall survival; GRFS, survival free from relapse, acute graft-versus-host disease grade III-IV and chronic graft-versus-host disease; aGVHD, acute graft-versus-host disease; cGVHD, chronic graft-versus-host disease; ATG, anti-thymocyte globulin; CMV, cytomegalovirus; MUD, HLA-matched (8/8 loci) unrelated donor; MSD, HLA-matched sibling donor; TBI, total body irradiation; CHT, chemotherapy; alloSCT, allogeneic stem cell transplantation; alloHSCT, allogeneic haematopoietic stem cell transplantation.
All models were adjusted for the following factors: ATG vs. no ATG, MUD vs. MSD, age (per 10 years), year of alloSCT, interval from diagnosis to alloHSCT, patient and donor sex, patient and donor CMV serostatus, reduced intensity versus myeloablative conditioning, TBI- vs. CHT-based conditioning. Only the effects of ATG and factors with p values < 0.05 have been reported.
Data are presented as hazard ratio (HR) ± 95% CI.

with alloPBSCT in CR1, we have demonstrated the beneficial effect of ATG in terms of increased chance of GRFS, reduced risk of grade III-IV aGVHD and overall and extensive cGVHD. Although its use was associated with increased risk of relapse, no significant effect on survival could be observed.

Impact of *in vivo* T-cell depletion with the use of ATG on results of alloHSCT was a subject of eight randomised trials in adults recruiting mainly patients with myeloid malignancies, while those with ALL constituted 0%–29% [12–16,22,23]. The proportion of patients with Ph+ ALL has not been reported.

The first two studies, conducted by Bacigalupo *et al.* [12,24] focussed on transplantations from MUD using bone marrow as a source of stem cells. Thymoglobulin (Sanofi) was shown to reduce the risk of cGVHD and was associated with improved lung function in long-term follow-up. Subsequent study by Finke *et al.* [13,25] regarded the use of Grafalon (Neovii) at the dose of 60 mg/kg for patients treated with MUD-HSCT using either peripheral blood stem cells (82%) or bone marrow. The use of ATG was associated with reduced risk of grade II-IV aGVHD and cGVHD while increased probability of GRFS. In the study by Walker *et al.* [14], MUD-HSCT recipients (88% of alloPBSCT) were randomly assigned to receive thymoglobulin or placebo. Reduced risk of both aGVHD and cGVHD was reported for the ATG arm with increased chance of being free form immunosuppressive therapy at 12 months. In a recently published study by Soiffer *et al.* [16] including patients with myeloid malignancies receiving MUD-HSCT, the addition of Grafalon was associated with reduce risk of grade II-IV aGVHD and moderate to severe cGVHD but also with increased risk of relapse, leading to lower probability of LFS and OS. Finally, the only study that focussed on recipients of alloPBSCT from MSD was reported by Kröger *et al.* [15]. The use of Grafalon was associated with reduced risk of cGVHD and increased probability of GRFS with no impact on relapse and survival.

Results of our analysis confirm the beneficial effect of the use of ATG with regard to reduction of the risk of GVHD. The association is particularly strong for cGVHD including its extensive form. This issue is

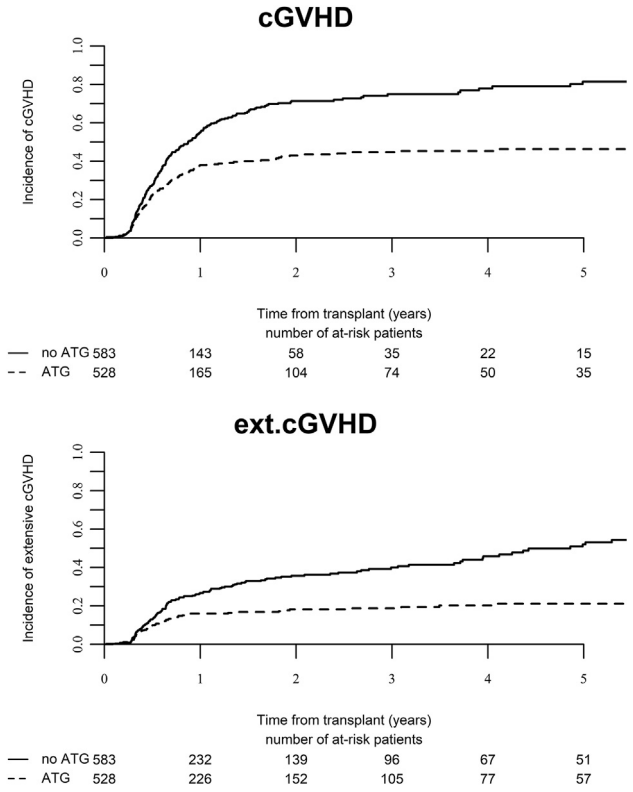

Fig. 1. The impact of the ATG on the incidence of overall chronic GVHD (cGVHD, $p_{Cox}<10^{-4}$) and extensive chronic GVHD (ext.cGVHD, $p_{Cox}<0.0001$). ATG, anti-thymocyte globulin.

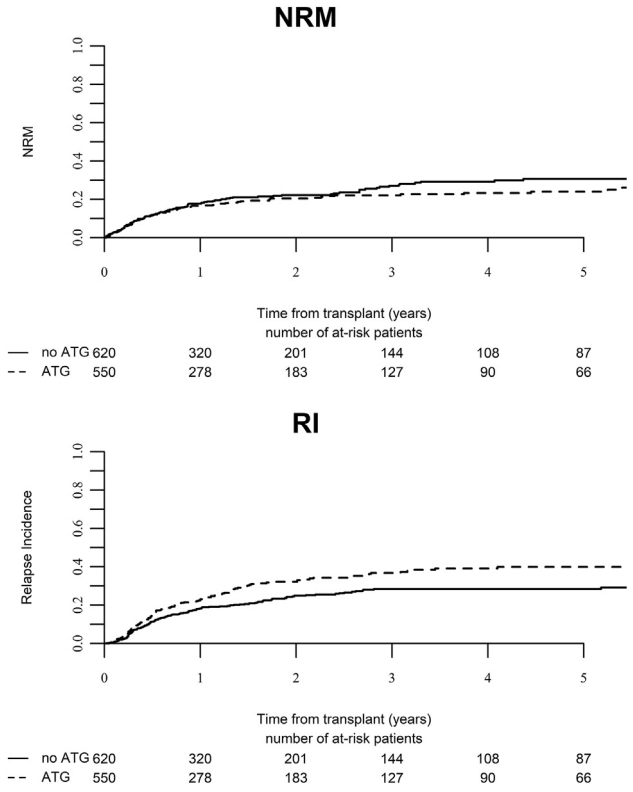

Fig. 2. The impact of ATG on non-relapse mortality (NRM, $p_{Cox} = 0.29$) and relapse incidence (RI, $p_{Cox} = 0.02$). ATG, anti-thymocyte globulin.

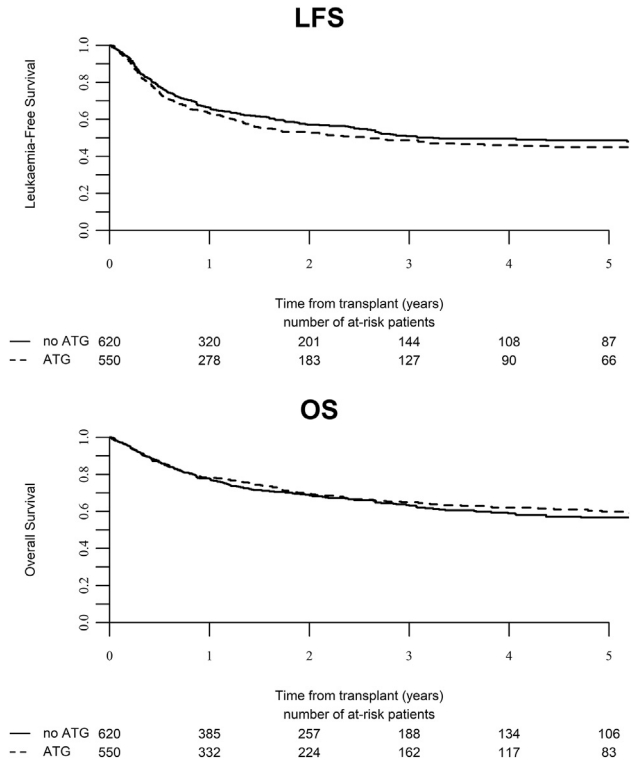

Fig. 3. The impact of ATG on leukaemia-free survival (LFS, $p_{Cox} = 0.3$) and overall survival (OS, $p_{Cox} = 0.62$). ATG, anti-thymocyte globulin.

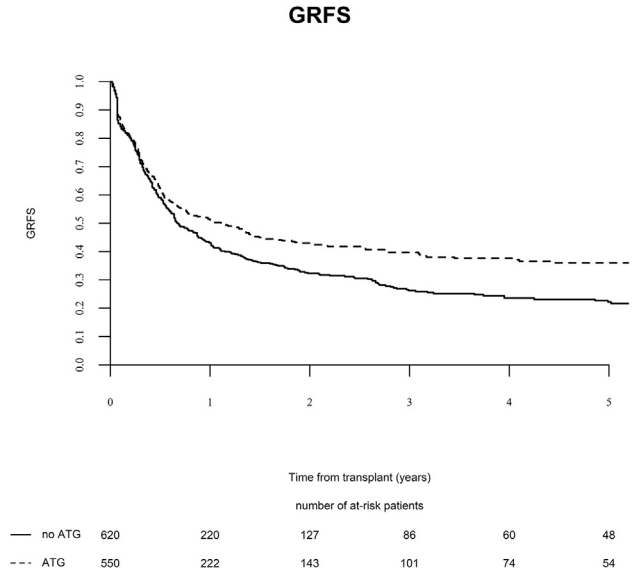

Fig. 4. The impact of the ATG on the probability of survival free from relapse, acute GVHD grade III-IV and chronic GVHD (GRFS, $p_{Cox} = 0.007$). ATG, anti-thymocyte globulin.

especially important using peripheral blood as a source of stem cells as this type of graft was shown to increase the risk of cGVHD [9]. As observed in randomised trials, the effect of the use of ATG on the incidence of GVHD did not convert into reduced risk of NRM. It could be explained by more profound and long-lasting

immunosuppression caused by ATG and increased risk of life-threatening infectious complications. Indeed, while in the no ATG group, GVHD was the most frequent cause of NRM and in the ATG group, infection-related deaths predominated.

The beneficial effect on GVHD was also partially counterbalanced by increased risk of relapse associated with the use of ATG. Although such effect was observed in only one of the randomised trials, increased risk of relapse has recently been reported by Czerw *et al.* [26] in a large retrospective study including patients with Ph-negative ALL. Therefore, it may be speculated that consequences of the use of ATG differ according to the diagnoses, and patients with ALL, irrespective of the status of Philadelphia chromosome, are particularly susceptible to its effects. This hypothesis is justified by the results of studies showing associations of the incidence of GVHD with reduced risk of disease recurrence. According to the recent analysis by Yeshurun *et al.* [17] including 5215 adults with ALL treated with alloHSCT in CR1 or second CR, the incidence of any grade of aGVHD or cGVHD was shown to significantly reduce the risk of relapse. Interestingly, in a study by Lee [27], including 74 patients with ALL and chromosomal abnormalities, mostly Ph+, the relapse rate at 5 years was 18% for those who developed chronic GVHD compared with 60% in remaining individuals ($p < 0.001$), suggesting that patients with Ph+ ALL are particularly susceptible to GVHD-related graft-versus-leukaemia reaction.

Despite increased risk of relapse, in the present study, the probability of GRFS was higher for patients in the ATG group compared with 'no ATG' group as the effect on GVHD was stronger than the impact on disease recurrence. Importantly, increased risk of relapse did not convert into reduced chance of survival. It may be speculated that with novel treatment approaches, some patients with ALL recurrence may still be effectively salvaged. Besides donor lymphocyte infusions and second alloHSCT, the options include the use of second- or third-generation TKIs and bi-specific T-cell enhancer—blinatumomab [28]. Assi *et al.* [29] reported safety and high efficacy of blinatumomab in combination with either dasatinib, ponatinib or bosutinib in a retrospective series of nine patients with Ph+ ALL relapsing after alloHSCT.

The results of our analysis showing increased risk of relapse among patients treated with ATG justify alternative approach, as recently proposed by the ALWP of the EBMT [30]. According to the expert consensus, patients with Ph+ ALL should be strictly monitored for the presence of minimal residual disease (MRD) before and after alloHSCT. Those MRD positive should be treated with TKIs according to the ABL-kinase domain mutation status, tumour burden and time of MRD reoccurrence. Patients with early MRD-negative status may either be treated prophylactically or pre-emptively. Both strategies have been documented feasible in a prospective trial by a German study group [31]. The use of post-transplant TKIs was associated with improved outcomes in a retrospective, registry-based study by Brissot *et al.* [32]. Therefore, it may be speculated that implementation of the aforementioned strategy may reduce the negative effect of ATG on relapse and strengthen the beneficial impact on GRFS.

Our study have some limitations, including potential bias related to unequal use of ATG according to the donor types and lack of data regarding the ATG brand and dose. As well, some data regarding the pretransplant molecular remission status and the use of TKI were missing. However, until randomised studies comparing ATG vs no ATG in patients with Ph+ ALL, our registry-based data are the only one available and are thus of major clinical implications.

Based on the results of the present study, we conclude that the use of ATG before alloPBSCT may be considered for patients with Ph+ ALL as it contributes to increased probability of GRFS, mainly by reducing the incidence of chronic GVHD. To diminish the risk of relapse, treatment should be MRD tailored, and prophylactic or pre-emptive use of TKIs after transplant should be considered. The optimal dosage and timing of ATG administration for patients with Ph+ ALL needs to be determined in further studies.

Conflict of interest statement

Sebastian Giebel and Tomasz Czerw received travel grants from Sanofi and Fresenius. Didier Blaise received honoraria from Sanofi. Mohamad Mohty received lecture honoraria and research support from Sanofi.

Acknowledgements

The authors kindly acknowledge the contribution of all EBMT centres reporting to the registry.

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