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# Anti-thymocyte globulin for graft-versus-host disease prophylaxis in patients with intermediate- or high-risk acute myeloid leukaemia undergoing reduced-intensity conditioning allogeneic stem cell transplantation in first complete remission – a survey on behalf of the Acute Leukaemia Working Party of the European Society for Blood and Marrow Transplantation

Rabbit anti-thymocyte globulins (ATG) are commonly used for prophylaxis of graft-versus-host disease (GVHD) when prescribed as part of conditioning therapy for allogeneic stem cell transplantation (Allo-SCT). A review emphasizing the beneficial ATG effect on GVHD incidence was recently published (Baron *et al*, 2017). Surprisingly, retrospective trials describing a dramatic chronic GVHD (cGVHD) rate reduction (Socie *et al*, 2011; Baron *et al*, 2014) and prospective, randomized trials confirming ATG anti-GVHD activity (Finke *et al*, 2009; Kroger *et al*, 2016; Walker *et al*, 2016; Soiffer *et al*, 2017) as well as a trial using a pre-emptive regimen (Bacigalupo *et al*, 2010) failed to demonstrate a statistically significant survival benefit of ATG use. Although the use of reduced-intensity conditioning (RIC) is growing, these patients are underrepresented in prospective ATG trials.

The current retrospective multicentre analysis, designed by the European Society for Blood and Marrow Transplantation (EBMT) Acute Leukaemia (AML) Working Party, aimed to explore the role of high and intermediate doses of ATG administered as part of RIC in adult high-risk AML patients transplanted while in first complete remission (CR1). The study was approved by institutional review boards of all the EBMT-affiliated centres and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines, relying on patients' informed consent authorizing the use of their personal information for research purposes. All of the participating centres are listed in Appendix S1.

The analysis included: adult AML patients (aged $\geq$ 18 years) with high-risk features (intermediate/poor-risk cytogenetics or secondary AML) who underwent a first RIC Allo-SCT (Baron *et al*, 2016) from either matched related or unrelated donors, while in CR1, between the years 2000 and 2014. Grafts could originate from peripheral blood or bone marrow of donors with 10/10 or 9/10 locus matching.

High-dose ATG was defined as >15 mg/kg of any brand or >6 mg/kg of ATG-thymoglobulin (ATG-T). The following doses were considered intermediate: 3–6 mg/kg of ATG-T, 7·5–15 mg/kg of ATG-Fresenius (ATLG) or <15 mg/kg of an unspecified brand. All other patients formed the control group.

Exclusion criteria were: previous Allo-SCT, any kind of *ex vivo* T cell depletion or alemtuzumab use. Patients with favourable cytogenetics were also excluded.

The primary endpoint of the study was GVHD-free relapse-free survival (GRFS) (Ruggeri *et al*, 2016). Secondary endpoints were: leukaemia-free survival (LFS), cGVHD, extensive cGVHD, relapse incidence (RI), non-relapse mortality (NRM) and OS.

Grading of acute and cGVHD was performed using established criteria. cGVHD was classified as limited or extensive according to standard criteria. Cumulative incidence of relapse and NRM were analysed as competing parameters. OS and LFS probabilities were calculated using the Kaplan–Meier estimate. All tests were two-sided with the type I error rate fixed at 0·05. Statistical analyses were performed with SPSS 19 (SPSS Inc., Chicago, IL, USA), and R 3.0.1 (R Development Core Team, Vienna, Austria) software packages.

Data on 1750 AML patients were included in this analysis (205 received high ATG doses, 358 – intermediate doses, and 1187 – no ATG). Groups were comparable in terms of patient and donor characteristics (Table I), although the proportion of patients with secondary AML was greater in the high-dose group. Following ATG prophylaxis, cGVHD rates at 1 and 3 years post-transplant were reduced by up to 50%, irrespective of the dose used (after 1 year: from 42·9% to 27·8% [24·6%]; after 3 years: from 48·7% to 31·6% [25·8%]; $P < 0·0001$). The corresponding values for extensive cGVHD were 22·9%, 13·9% and 10·9% after 1 year and 28·6%, 16·4% and 13·6% after 3 years (Table II). This reduction in cGVHD rate was reflected in GRFS improvement at both 1 and 3 years of follow-up (from 41·3% to 48% [49·7%] and from 29·3% to 37·3% [36%], respectively; $P = 0·0069$). The addition of ATG to conditioning regimens did not affect NRM, OS or LFS (Table II). Notably, ATG was associated with a rise in RI both at 1 and 3 years post-transplant, although this difference did not reach statistical significance (Table II).

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**Table I.** Patient characteristics.

| Variable | No ATG or dose <3 or 7·5 mg/kg ($n$ = 1187) | ATG dose 3–6 or 7·5–15 mg/kg ($n$ = 358) | ATG and dose >6 or 15 mg/kg ($n$ = 205) | All patients ($n$ = 1750) | $P$ value |
|---|---|---|---|---|---|
| Follow-up for survivors, months | | | | | |
| Median (range) | 52·7 (0·0–177·3) | 27·1 (0·0–159·1) | 42·9 (0·7–156·6) | 44·6 (0–177·3) | <0·0001 |
| Age at transplant, years | | | | | |
| Median (range) | 57·0 (18·1–75·8) | 58·0 (27·1–70·3) | 56·6 (20·5–70·4) | 57·3 (18·1–75·8) | 0·054 |
| Time from diagnosis to transplant, days | | | | | |
| Median (range) | 146·0 (9·0–451·0) | 166·0 (43·0–434·0) | 153 (43–11 248) | 153 (9–11 338) | <0·0001 |
| Year of transplant | | | | | |
| Median (range) | 2008 (2000–2014) | 2011 (2000–2014) | 2009 (2000–2014) | 2009 (2000–2014) | <0·0001 |
| Patient gender, $n$ (%) | | | | | |
| Male | 636 (53·6) | 199 (55·6) | 107 (52·2) | 942 (53·8) | 0·71 |
| Female | 551 (46·4) | 159 (44·4) | 98 (47·8) | 808 (46·2) | |
| Donor gender, $n$ (%) | | | | | |
| Male | 606 (51·4) | 202 (56·4) | 112 (54·6) | 920 (52·8) | 0·22 |
| Female | 572 (48·6) | 156 (43·6) | 93 (45·4) | 821 (47·2) | |
| Sex mismatch, $n$ (%) | | | | | |
| Female to male | 297 (25·2) | 81 (22·6) | 48 (23·4) | 426 (24·5) | 0·57 |
| Other combinations | 881 (74·8) | 277 (77·4) | 157 (76·6) | 1315 (75·5) | |
| Donor CMV, $n$ (%) | | | | | |
| Negative | 402 (35·0) | 158 (44·3) | 85 (42·5) | 645 (37·8) | 0·002 |
| Positive | 746 (65·0) | 199 (55·7) | 115 (57·5) | 1060 (62·2) | |
| Patient CMV, $n$ (%) | | | | | |
| Negative | 323 (28·1) | 136 (38·2) | 65 (31·9) | 524 (30·6) | 0·001 |
| Positive | 828 (71·9) | 220 (61·8) | 139 (68·1) | 1187 (69·4) | |
| CMV match patient/donor, $n$ (%) | | | | | |
| −/− | 197 (17·3) | 95 (26·8) | 43 (21·6) | 335 (19·8) | 0·003 |
| −/+ | 121 (10·6) | 41 (11·5) | 21 (10·6) | 183 (10·8) | |
| +/− | 201 (17·7) | 62 (17·5) | 41 (20·6) | 304 (18) | |
| +/+ | 619 (54·4) | 157 (44·2) | 94 (47·2) | 870 (51·4) | |
| Stem cell source, $n$ (%) | | | | | |
| BM | 136 (7·8) | 111 (9·4) | 11 (5·4) | 136 (7·8) | 0·009 |
| PB | 1606 (91·8) | 1070 (90·1) | 193 (94·1) | 1606 (91·8) | |
| BM+PB | 8 (0·5) | 6 (0·5) | 1 (0·5) | 8 (0·5) | |
| Cytogenetics, $n$ (%) | | | | | |
| Intermediate | 673 (56·7) | 200 (55·9) | 93 (45·4) | 966 (55·2) | 0·002 |
| Poor | 185 (15·6) | 62 (17·3) | 28 (13·7) | 275 (15·7) | |
| Secondary AML, $n$ (%) | 329 (27·7) | 96 (26·8) | 84 (41) | 509 (29·1) | |
| Use of TBI, $n$ (%) | | | | | |
| No | 697 (58·7) | 350 (97·8) | 167 (81·5) | 1214 (69·4) | |
| Yes | 490 (41·3) | 8 (2·2) | 38 (18·5) | 536 (30·6) | |

AML, acute myeloid leukaemia; ATG, antithymocyte globulin; BM, bone marrow; CMV, cytomegalovirus; PB, peripheral blood; TBI, total body irradiation.

In multivariate analysis, only patient age, cytogenetics and donor cytomegalovirus status significantly affected OS and LFS. ATG administration was identified as a significant factor influencing cGVHD, RI, NRM and GRFS, regardless of the prescribed dose. Female-to-male transplant was associated with higher cGVHD rates and decreased GRFS. ATG use was related to reduction in the extensive cGVHD rate, with a hazard ratio of 0·54 for intermediate and 0·4 for high dose ($P < 0·001$).

Although the specific ATG brand used was not recorded for many patients, it could be assumed that all patients in the low-dose group received ATG-T, whereas patients receiving doses >40 mg/kg could be considered as treated with ATLG. While the latter group included only 41 patients, it is worth mentioning due to very low cGVHD and extensive cGVHD rates (21·8% and 5·5%) at both 1 and 3 years. This achievement was associated with GRFS increase to 56·7% and 42·3% for 1 and 3 years, without OS benefit.

Our analysis has shown that in the RIC context, ATG administration is associated with decreased GVHD incidence and severity. It is intriguing that the therapy which



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**Table II.** Effects of different ATG doses on patient outcome.

| | Follow-up (years) | No ATG +/− low dose (%), HR [95% CI] | Intermediate ATG dose (%), HR [95% CI] | High ATG dose (%), HR [95% CI] | *P* value |
|---|---|---|---|---|---|
| LFS | 1 | 62·4 [59·6–65·3] | 60·7 [55·6–66·2] | 60·2 [53·7–67·6] | 0·584 |
| | 3 | 49·8 [46·9–53] | 48·5 [43–54·6] | 46·3 [39·4–54·3] | |
| OS | 1 | 69·4 [66·8–72·2] | 72·9 [68·2–77·9] | 71·8 [65·7–78·5] | >0·99 |
| | 3 | 54 [51·1–57·1] | 54·2 [48·7–60·3] | 54·9 [47·9–62·9] | |
| RI | 1 | 25·8 [23·2–28·3] | 30·3 [25·4–35·3] | 30·4 [24·1–37] | 0·0725 |
| | 3 | 33·3 [30·5–36·1] | 38·4 [32·9–43·9] | 40·9 [33·7–48] | |
| NRM | 1 | 11·8 [10–13·8] | 9 [6·2–12·4] | 8·5 [5·2–12·9] | 0·137 |
| | 3 | 16·8 [14·6–19·1] | 13·1 [9·6–17·2] | 11·7 [7·5–16·8] | |
| CGVHD | 1 | 42·9 [39·9–45·9] | 27·8 [23–32·8] | 24·6 [18·6–31] | <0·0001 |
| | 3 | 48·7 [45·6–51·7] | 31·6 [26·4–36·9] | 25·8 [19·7–32·4] | |
| cGVHD ext. | 1 | 22·9 [20·4–25·5] | 13·9 [10·3–17·9] | 10·9 [6·9–15·9] | <0·0001 |
| | 3 | 28·6 [25·9–31·4] | 16·4 [12·4–20·8] | 13·6 [9–19·2] | |
| GRFS | 1 | 41·3 [38·5–44·3] | 48 [42·9–53·8] | 49·7 [43–57·5] | 0·0069 |
| | 3 | 29·3 [26·7–32·2] | 37·3 [32·1–43·4] | 36 [29·4–44·1] | |

95% CI, 95% confidence interval; ATG, antithymocyte globulin; cGVHD, chronic graft-versus-host disease; cGVHD ext, extensive chronic graft-versus-host disease; HR, hazard ratio; LFS, leukaemia-free survival; NRM, non-relapse mortality; OS, overall survival; RI, relapse incidence.

spares a marked proportion of patients from devastating extensive cGVHD is not associated with OS improvement. Indeed, due to the noteworthy reduction in extensive GVHD rate, despite an increase in relapse rate and NRM, the composite GRFS endpoint was improved by 7–8%. Most important is our finding that intermediate and high doses of ATG have similar effects. This result emphasizes the need for comparisons of patients receiving different ATG doses and the use of a homogenous control group receiving no ATG at all.

Our findings should be cautiously interpreted due to limitations of registry-derived data that may be affected by patient selection biases and missing data. We were unable to analyse the effect of different brands of ATG separately. However, the very good outcome of patients receiving doses >40 mg, assumed to be ATLG, warrants further studies of this regimen.

In the current study, ATG incorporation in RIC regimens significantly improved GRFS, which is definitely a desirable outcome from patient's perspective. Overall, ATG is a powerful tool for GVHD prophylaxis. Further studies are required to determine whether the use of a specific ATG dose or brand could improve the clinical outcome.

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Ofran: Received honoraria for lectures and advisory board contributions from Amgen, Roche and Novartis. Beohou, Labopin, Cornelissen, de Groot, Huynh, Maertens, Baron, Mohty and Nagler: None. Blaise: Honoraria from Sanofi Gemzyme and Pierre Fabre Medicaments. Socié: Received lecture fees from Fresenius and Neovi Pharma.

## Conflict of Interest Statement

There are no conflicts to declare.

## Contribution of coauthors

Ofran: designed the study, interpreted the data, wrote the manuscript, approved the final version of the manuscript. Beohou and Labopin: designed the study, performed the study statistics, interpreted the data, approved the final version of the manuscript. Blaise, Cornelissen, de Groot, Socié, Huynh, Maertens, Baron and Mohty: provided clinical data, edited the manuscript, approved the final version of the manuscript. Nagler: designed the study, interpreted the data, edited the manuscript, approved the final version of the manuscript.

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## Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Appendix S1.** The List of Participating Centers.

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