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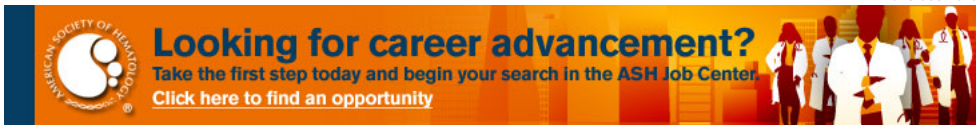

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Higher Doses of Antithymocyte Globulin (ATG) Increase the Risk of Relapse in Acute Myeloid Leukemia (AML) Patients Undergoing Matched Related Donor Allogeneic Transplantation in First Complete Remission (CR1): An Analysis from the Acute Leukemia Working Party of EBMT

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Abstract

The use of ATG as part of the reduced-intensity conditioning regimen for AML is still controversial especially in the setting of matched related donor (MRD) allogeneic hematopoietic stem cell transplantation (alloHSCT). A previous study suggested that the use of ATG reduced the incidence of graft versus host disease (GVHD) but increased the risk of relapse when a MRD is used, leading to worse outcome compared to patients who did not receive any in vivo T-cell depletion (CIBMTR data, Soiffer et al., Blood 2011). In contrast, the EBMT series, focused on AML patients undergoing alloHSCT from MRD in CR1, showed that the use of ATG reduced the incidence of GVHD without increasing the risk of relapse (Baron et al., BMT 2014). These discordant conclusions could be explained by the different median doses of ATG used, 7 and 5 mg/kg in the CIBMTR and EBMT studies, respectively. Thus, we hypothesized that the dose and the type of ATG are critical issues and could be a major determinant of outcome after alloHSCT. Here, we investigated the impact of ATG (Thymoglobulin) dose on cumulative incidences of GVHD, non-relapse mortality (NRM), relapse (CIR), leukemia-free (LFS) and overall survival (OS).

Data of patients with the following criteria were collected from the EBMT registry: alloHSCT between January 2000 and February 2013; AML in CR1; peripheral blood stem cells from MRD as graft source; RIC regimen; use of ATG (Thymoglobulin) as part of the RIC regimen.

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We analyzed 334 consecutive patients with a median age of 56 years (range, 19-70). Fifty-eight (17%) patients had unfavorable cytogenetics and 238 (71%) received a busulfan-based RIC regimen. Most patients (95%) received cyclosporine A as GVHD prophylaxis, while mycophenolate mophetil (MMF) was added to 99 patients (30%). ATG was given at the dose of 6 mg/kg or more (high dose group, median dose: 7.5 mg/kg, range: 6-10.5) in 71 patients (21%) while 263 patients (79%) received less than 6 mg/kg total dose (low dose group, median dose: 5 mg/kg, range: 2-5.5). Patients in the higher dose group were more frequently transplanted before 2009, received more frequently a RIC regimen without busulfan and were more frequently given MMF in GVHD prophylaxis. Age, time from diagnosis to alloHSCT and cytogenetic risk groups were equally distributed according to both high and low ATG dose groups.

In multivariate analysis after adjustment for age (<=55 vs. >55 years), transplant period (2000-08 vs. 2009-13), cytogenetics (unfavorable vs. other), RIC regimen (busulfan-based vs. other) and GVHD prophylaxis (MMF vs. no MMF) showed no significant impact of high ATG dose (low dose was considered as the reference group) on the incidence of both grade II-IV acute (OR=0.996 [95%CI, 0.561-1.767]; p=0.989) and chronic GVHD (HR=0.977 [95%CI, 0.543-1.759]; p=0.939). Similarly, ATG dose did not influence the cumulative incidence of NRM (HR=1.202 [95%CI, 0.467-3.093]; p=0.703). With a median follow up of 36 months, high ATG dose significantly increased the CIR (HR=2.298 [95%CI, 1.328-3.977]; p=0.003, **Figure A**), leading to significantly shorter both leukemia-free (HR=1.904 [95%CI, 1.186-3.058]; p=0.008) and overall survival (HR=1.711 [95%CI, 1.030-2.844]; p=0.038, **Figure B**).

In conclusion, these results suggest that ATG dose is a determinant factor for outcome. ATG total dose below 6 mg/kg is likely sufficient for GVHD prophylaxis, with no additional benefit for using the higher ATG doses. In contrast, a higher ATG dose (6 mg/kg and more) will likely impair outcome of patients due to a significant increase of the relapse risk. Therefore, in the setting of CR1 AML patients undergoing RIC alloHSCT from MRD, lower ATG doses (<6 mg/kg total dose) could be safely used and can allow for better GVHD control without impairing the overall outcome. These results may differ in patients transplanted for other diseases than CR1 AML. Further comparative prospective studies could be helpful to better identify the optimal ATG dose in different setting of AML.

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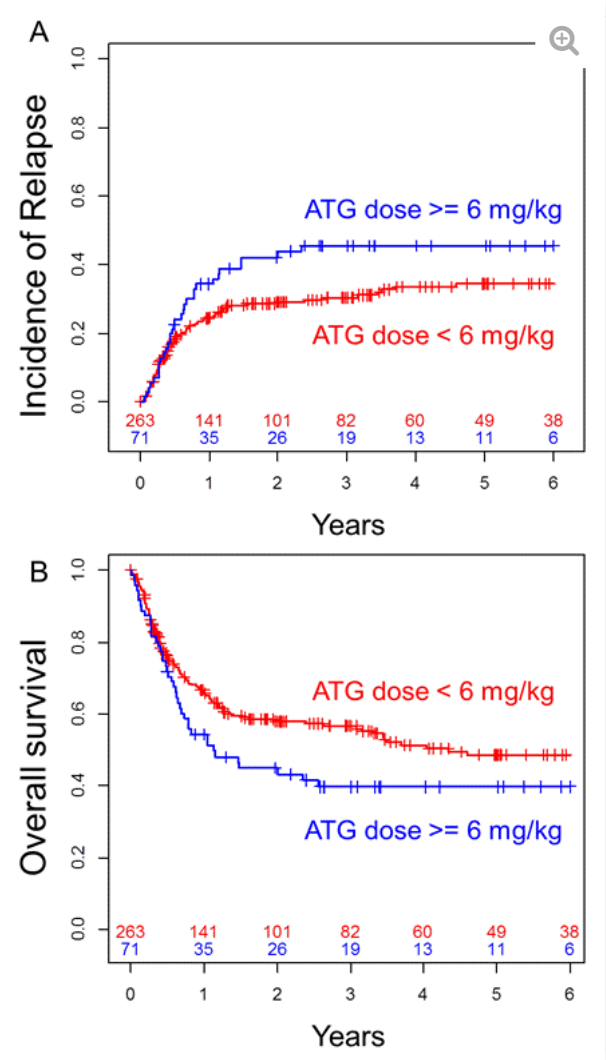

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