GvHDHub

Impact of antithymocyte globulin and total body irradiation on outcomes of allogeneic hematopoietic cell transplantation in patients with acute myeloid leukemia

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Fit patients with acute myeloid leukemia (AML) can be treated through allogeneic hematopoietic cell transplantation (allo-HCT), along with a myeloablative conditioning (MAC) regimen. However, the use of such treatment comes with the risk of graft-*versus*-host disease (GvHD).[1]

Chronic GvHD (cGvHD) is known to decrease quality of life, and is the leading cause of mortality in long-term survivors after allo-HCT.[2] A number of phase II studies[3] have reported an association between the use of antithymocyte globulin (ATG) in patients receiving unmanipulated bone marrow (BM) grafts after MAC, with decreased acute GvHD (aGvHD), cGvHD and an improved quality of life.

So far, prospective randomized phase II studies have reported a decreased rate of cGvHD when inducing *in vivo* T cell depletion (TCD) with ATG. However, comparison of results is difficult due to heterogeneous patient populations and infrequent use of total body irradiation (TBI)-based ablative regimens. Arnon Nagler, from Tel Aviv University, Israel, and colleagues, conducted a retrospective analysis on 724 patients to explore the impact of ATG together with TBI-based MAC regimen, testing the hypothesis that ATG prior to allo-HCT decreases the risk of GvHD.

The end-points of the study were engraftment as well as the incidence and severity of cGvHD and aGvHD. Other endpoints of the study included primary disease relapse incidence (RI), non-relapse mortality (NRM), leukemia-free survival (LFS), OS, and, GvHD- and relapse-free survival (GRFS).

Study design

The retrospective study used data from the acute myeloid leukemia (AML) Working Party of the European Society for Blood and Marrow Transplantation (EBMT) registry. Included in the analysis were 724 patients ≥18 years of age with AML, who had undergone an initial allo-HCT from a matched sibling or 9/10 or 10/10 matched unrelated donors (MUD), after TBI-based MAC regimen, between 2008 and 2016. The outcomes of 215 patients treated with ATG as GvHD prophylaxis, were compared to 473 patients who had not received ATG, in order to understand whether ATG treatment reduces the severity of GvHD while maintaining graft-*versus*-leukemia (GvL) effect.

Characteristics from both the recipients and the donors were collected and analyzed, including age, sex, disease status, conditioning regimen, the interval from diagnosis to transplant, and use and a dose of ATG for pretransplant *in vivo* TCD.

Table 1: Baseline characteristics

	ATG group (n=251)	Non-ATG group (n=473)	*P*
Age at allo-HCT (years)	39 (18.1–67.7)	39.6 (18.1–62.1)	0.34
Patient sex			
Male	141 (56.18)	251 (53.07)	
Female	110 (43.82)	222 (46.93)	
Donor type			
MSD	27 (10.76)	385 (81.4)	<0.01
UD 10/10	164 (65.34)	72 (15.22)	
UD 9/10	60 (23.90)	16 (3.38)	
Conditioning regimen			
Cy-TBI	212 (84.46)	442 (93.45)	<0.001
Flu-TBI	39 (15.54)	31 (6.55)	

No significant differences in patient characteristics were observed between the ATG group and the non-ATG group. There was also no difference in terms of the cytogenetic risk category based on the European Leukemia Net Stratification between both groups.[4]

Results

The median follow-up was 59 months in the non-ATG group (interquartile range [IQR], 28–83), and 58 months in the ATG group (IQR, 24–83).

Between the two groups, no difference was observed in the rate of engraftment (99% in both groups), while the median time to neutrophil engraftment was longer in the ATG group (19 days *vs* 17 days; p <0.001). Three patients in the non-ATG and two patients in the ATG group died before engraftment (day 28).

Univariate analysis showed that in the ATG group *in vivo* TCD was significantly associated with a reduced risk of grade II-IV and grade III-IV aGvHD, with 100-day cumulative incidences being 33% *vs* 24%, and 13% *vs* 7%, in the non-ATG and ATG groups, respectively.

Multivariate analysis showed TCD in the ATG group was independently associated with a decreased risk for grade II-IV aGvHD and grade III-IV aGvHD.

Two-year cumulative incidences of overall and extensive cGvHD were significantly less in the ATG group than in the non-ATG group (overall, 46% *vs* 34%; extensive, 22% *vs* 16%).

Two-year NRM and the cumulative incidence of relapse was similar between both groups. Aside from GvHD, the main cause of death from NRM in the non-ATG and ATG groups were infections (21 *vs* 14 patients), and veno-occlusive disease (4 *vs* 1 patient). Relapse was the main cause of death in both groups of patients (53% in the non-ATG group, and 47% in the ATG group).

Table 2: Two-year results in the non-ATG and ATG groups

Two-year	**Whole cohort**	**ATG**	**Non-ATG**	***p***
Cumulative incidence of overall cGvHD		46%	34%	0.003
Cumulative incidence of extensive cGvHD		22%	16%	0.01
NRM	16% (95% CI, 13.6–19.1)	17%	16%	
Cumulative incidence of relapse	24.5% (95% CI, 22.2–28.8)	26%	25%	
OS	63.2% (95% CI, 59.5–66.9)	62%	64%	
LFS*	58% (95% CI, 54.5–62.1)	57%	59%	

*LFS, leukemia-free survival

Table 3: Major causes of death among the ATG and the non-ATG groups

Cause of death	ATG group (n=101, %)	Non-ATG group (n=192, %)
Cardiac toxicity	1	2
Hemorrhage	4	0
Graft failure	0	1
Veno-occlusive disease	1	4
Infection	14	21
Interstitial pneumonitis	1	5
GvHD	20	42
Relapsed AML	47	100
Second malignancy	0	3
Other NRM	11	9
Missing	2	5

Conclusion

The data from this study indicates that TBI in combination with ATG is an effective conditioning regimen for allo-HCT in patients with AML. Results showed that the incorporation of ATG in TBI-based MAC for allo-HCT in patients with AML, resulted in lower GvHD rates without increasing the risk of relapse or NRM.

References

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