ENDOTHELIAL DYSFUNCTION AND RISK OF ACUTE GRAFT-VERSUS-HOST DISEASE AFTER ALLOGENEIC STEM CELL TRANSPLANTATION: END-GAME PROSPECTIVE STUDY FINAL RESULTS

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INTRODUCTION

Endothelial dysfunction has been increasingly correlated to the very early phases of acute graft-versus-host-disease (aGVHD) with endothelial cells acting both as starting elements of the inflammatory process and as a target of allo-reactive donor T cells ("endothelial GVHD").

AIM

This observational prospective single-center study investigates the role of endothelial dysfunction at the time of allogeneic hematopoietic stem cell transplantation (HSCT) in predicting the incidence of aGVHD. Inclusion criteria were: adult patients (≥18 years old) undergoing their first HSCT for any hematological disease, from any donor and any stem cell source. The primary endpoint was cumulative incidence of aGVHD at day 100 post-HSCT.

METHOD

- Levels of circulating endothelial cells (CECs), circulating endothelial progenitors (CEPs) and some soluble biomarkers (plasminogen activator inhibitor-1 [PAI-1], vascular endothelial growth factor [VEGF-A], angiopoietin-2 [ANG-2], soluble VCAM [sVCAM-1]) were assessed on peripheral blood samples collected on the day of HSCT (T0).
- CECs and CEPs were identified by flow cytometry according to Lanuti et al. 2018 and Mancuso et al. 2020 protocol, respectively.
- CECs >30 cells/ml were considered elevated. Since a normal reference range for CEPs has not yet been established, they were divided into tertiles.
- Soluble biomarkers were analyzed using the automated microfluidic analyzer ELLA (BioTechne, Minneapolis, USA), according to the manufacturer's protocol and results expressed by pg/ml.
- Statistical analysis was performed in accordance with the EBMT recommendations. As this is a proof-of-concept study, p-values <0.2 were considered significant.

RESULTS

	Total
	N=51
Age (years)	54.3 (38.6-63.5)
Median follow-up (months)	23 (18-28)
Sex	
• Female	29 (56.9%)
• Male	22 (43.1%)
Ethnicity	
• Caucasian	46 (90%)
• Indiana, Pakistani, Bangladesh or other South Asian ethnic group	2 (4%)
• European Blacks / African Blacks / Other Black Ethnic Groups	1 (2%)
• European Arabs / Other Arab ethnic groups	2 (4%)
Male recipient/female donor (M/F)	3 (6%)
Donor	
• Identical sibling	4 (8%)
• Haploidentical	12 (24%)
• Matched unrelated	19 (37%)
• Mismatched unrelated	16 (31%)
Stem cells source	
• Bone marrow (BMSC)	4 (8%)
• Peripheral blood (PBSC)	47 (92%)
Diagnosis: Acute Leukemia	31 (61%)
Disease risk index (DRI) High/Very High	16 (31%)
Disease status at transplant: CR	36 (78%)
HCT-CI (Sorror score) High	16 (31%)
Myeloablative conditioning	44 (86%)
GVHD prophylaxis	
• Post-Transplant Cyclophosphamide (PT-CY)	24 (47%)
• ATG-based	25 (49%)
• CSA + methotrexate full dose	2 (4%)

Table 1. Patients' characteristics.

Patients and transplant characteristics are shown in Table 1.

After a median follow-up of 23 months (IQR, 18-28), a total of 29 (57%) patients developed acute GVHD (14/51, 27% grade 2 or higher), for a 100-day cumulative incidence of aGVHD of 47% (95% confidence interval [95%CI], 33-60%). Two-year cumulative incidence of chronic GVHD, non-relapse mortality (NRM), cumulative incidence of relapse (CIR) and overall survival (OS) were: 27% (95%CI, 15-40%), 15% (95%CI, 6-26%), 10% (95%CI, 4-20%) and 78% (95%CI, 63-87%).

Median CECs at the time of HSCT (T0) were 46 cells/ml (IQR, 28-80 cells/ml). In univariable analysis, CECs >30 cells/ml (n=36, 71%) were found to be associated with higher risk of aGVHD of any grade (SHR=3.0, 95%CI 1.0-9.0, p=0.053). Conversely, CEPs did not associate with cumulative incidence of aGVHD (p=0.631).

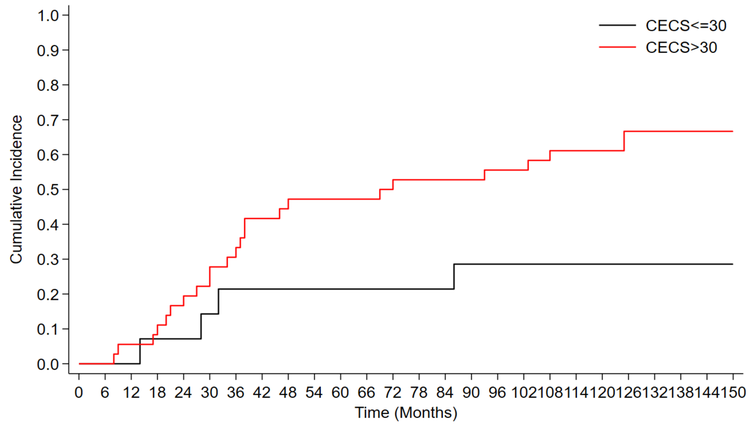

Figure 1. Cumulative incidence of acute GVHD in patients with CECs> 30 cells/ml vs CECs < 30 cells/ml at T0 (day of transplant), p= 0,120.

Among soluble endothelial biomarkers at T0, VEGF-A (low/normal/high 94%/6%/0%), ANGP2 (low/normal/high 62%/20%/18%) and sVCAM-1 (low/normal/high 34%/48%/18%) showed no association with cumulative incidence of aGVHD at univariable analysis (all p>0.2). PAI-1 was not evaluable, as all the patients presented values below the range of reference.

In multivariable analysis, after adjustment for the following variable Karnofsky <90%, increased CECs at T0 were confirmed as independent risk factor for aGVHD (SHR 2.5, 95%CI 0.8-8.2, p=0.120).

CONCLUSIONS

Overall, our findings suggest that early endothelial damage may contribute to the risk of aGVHD. Identifying endothelial stress at the time of transplantation could therefore guide the selection and adjustment of GVHD prophylaxis. Larger study cohorts are warranted to confirm our preliminary results.

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