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701.EXPERIMENTAL TRANSPLANTATION: BASIC AND TRANSLATIONAL

Evaluation of Circulating Endothelial Cells (CECs) As Marker of Endothelial Damage in Allo-Transplanted Patients at High Risk of Hepatic Veno-Occlusive Disease/Sinusoidal Obstruction Syndrome (VOD/SOS): The Cecinvod Study

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INTRODUCTION

Sinusoidal obstruction syndrome (SOS), also known as veno-occlusive disease (VOD), is a potentially fatal complication after allogeneic stem cell transplantation (alloSCT). Identifying a predictive biomarker for VOD has been challenging. Since endothelial injury is considered one of the main pathogenic factors for VOD onset, with the CECinVOD prospective study we aimed to evaluate Circulating Endothelial Cells (CEC) in allo-transplanted patients (pts) at higher risk to develop VOD.

METHODS

From October 2020 to November 2022, 150 pts have been enrolled in the CECinVOD study from 11 Italian Bone Marrow Transplantation Units. All pts must be older than 18 years and undergoing myeloablative alloSCT. CECs were detected using the CellSearch system, the FDA-approved immunomagnetic selection approach incorporating ferrofluid nanoparticles (anti CD146) and fluorophore-labelled antibodies (anti CD105, CD45 and DAPI). CEC were defined as CD146+, CD105+, DAPI+ and CD45-. CEC were collected at the following timepoints: before conditioning regimen (T0), at the end of conditioning regimen and before alloSCT (T1), at the time of neutrophils engraftment (T2), and 7-10 days after engraftment (T3). In pts who developed VOD, additional timepoints were collected as follows: at any time of suspected or proven VOD onset (T4), and

then weekly during Defibrotide treatment (T5-T8). SOS/VOD was defined according to the 2016 European Group for Blood and Marrow Transplantation criteria.

RESULTS

Pts' main characteristics are summarized in Table 1. Six out of 150 pts (4%) developed VOD during the follow up (4 "severe", and 2 "very severe"). All pts were treated with Defibrotide, obtaining a complete remission in 5 of them, while 1 pt died due to VOD complications. Pts receiving TBI-based regimen were more likely to develop VOD compared to those receiving Treosulfan (10 to 14 g/m2) or Busulfan ev (9.6 to 12.8 mg/kg) (p 0.08). Similarly, higher baseline levels of bilirubin were associated with a higher incidence of VOD (p 0.08).

Considering the CECs analysis, 615 samples were evaluated. At the enrollment, CECs levels were not related with any of clinical characteristics analyzed, except for the number of previous treatments. Indeed, those pts with 2 or more previous lines of treatments had higher levels of CECs (OR=0.53; $p<0.001$). Considering the different timepoints, conditioning regimen and alloSCT result in higher levels of CECs. Thus, CEC were higher at T1 than at T0 (p 0.02), as well as they were even higher at T2 than at T1 ($p<0.0001$) (Fig.1). Conversely, no significant differences have been observed between T3 and T2. No other clinical characteristic was correlated with CEC counts at the different timepoints. Pts who developed VOD had higher median levels of CEC at all the timepoints analyzed, but this difference has not achieved statistical significance, probably due to the low number of pts in the VOD group. At VOD onset, the pts always had an increase in CEC levels compared with the previous timepoint. After defibrotide treatment, the CEC levels increased in the first week, while they progressively decreased during the VOD treatment (T6 and T7, -50,7% and -71,5%, respectively).

Recently, another endothelial activation marker has been considered: the Easix score. We didn't find any relationship between the Easix score at transplant and the VOD onset, even if a trend may be observed. We also investigated whether the CEC levels may be related with Easix score, but we didn't find any relationship at each timepoint.

Interestingly, in a subgroup of pts CECs have been observed as a cluster of multiple cells. This data is firstly described in alloSCT. Its functional significate remains unclear, but we found a relationship between CECs cluster and the number of CECs ($p < 0.001$).

CONCLUSIONS

The incidence of VOD in our prospective study was low with respect to the one reported in the literature. This can be explained by the changes in alloSCT from the past (better selection of the pts, lower use of TBI, higher use of reduced intensity regimen) and the retrospective nature of most of the previous reports. We show that CECs can be considered reliable marker of endothelial damage in alloSCT pts, highlighting the impact of previous treatments, the conditioning regimen, and allo-SCT itself. Increased CEC level may be helpful to confirm VOD diagnosis, as well as their monitoring may be useful to evaluate the response to the treatment for VOD.

Disclosures Polverelli: *Novartis:* Honoraria; *Abbvie:* Honoraria; *GSK:* Honoraria; *BMS:* Honoraria. **Bonifazi:** *Sanofi:* Honoraria; *Neovii:* Honoraria. **Malagola:** *Biotest, MSD:* Consultancy, Honoraria. **Russo:** *MSD, Novartis, Gilead, BMS, Medac:* Honoraria; *Medac, Abbvie, MSD, Jazz Pharma, Gilead, Novartis:* Membership on an entity's Board of Directors or advisory committees.

	Patiens with VOD	Patients without VOD	p-value
Number (% of total)	**6 (4)**	**144 (96)**	
Age (median, range)	52,7 (28 - 68)	48,2 (18 - 69)	0.39
Sex (Male, n, %)	1 (17)	51 (35)	0.67
CECs			
CECs @ T0 (median; range)	69 (16-157)	36 (1-3698)	0.23
CECs @ T1 (median; range)	82.5 (29-315)	48 (3-168)	0.26
CECs @ T2 (median; range)	151 (48-289)	98 (4-481)	0.58
CECs @ T3 (median; range)	149 (52-264)	109 (7-1180)	0.35
CECs T1vsT0 (relative increase %)	104.8 (-81 to 343)	35.6 (-100 to 48000)	0.61
CECs T2vsT1 (relative increase %)	7.2 (-100 to 660)	111.3 (-100 to 8800)	0.15
CECs T4vsT2 (VOD) VS T3vsT2 (relative increase %)	114.7 (-19 to 283.3)	- 3.1 (-100 to 7162)	0.11
CECs T5vsT4 (relative increase %)	92.57 (3,9 to 221,4)	N.A.	
CECs T6vsT5 (relative increase %)	-50,7 (-71,14 to 32,6)	N.A.	
CECs T7vsT6 (relative increase %)	-71,5 (-49,1 to -99)	N.A.	
Disease (n, %)			
AML	1 (17)	84 (58)	0.09
MPN	2 (33)	16 (11)	0.15
ALL	2 (33)	25 (17)	0.29
MDS	0 (0)	18 (12,5)	>0.99
NHL/MM	1 (17)	1 (1)	0.08
State of disease			
CR	4 (67)	97 (67)	>0.99
≥ 2 CR	0 (0)	5 (3)	>0.99
PR	1 (17)	11 (8)	0.37
SD/PD	0 (0)	22 (15)	>0.99
Number of previous line			
0 -1	1 (17)	70 (48)	0.21
2	2 (33)	43 (30)	>0.99
≥ 3	3 (50)	31 (22)	0.10
Previous Cardiovascular complications	1 (17)	15 (10)	0.50
Cardiovascular risk factor	1 (17)	16 (11)	0.52
Donor Type (n, %)			
Unrelated donor	2 (33)	93 (65)	0.19
HLA-mismatched donor	4 (67)	49 (34)	0.19
Stem-cell source (n, %)			
Peripheral blood	6 (100)	137 (95)	>0.99
Bone marrow	0 (0)	3 (2)	>0.99
Cord blood	0 (0)	4 (3)	>0.99
CMV serology IgG D/R (on 134 pts)			
IgG+/+	1 (17)	69 (48)	0.19
IgG+/-	0 (0)	14 (10)	>0.99
IgG-/-	2 (33)	10 (7)	0.06
IgG-/+	2 (33)	37 (26)	0.63
Sorror HCT-CI			
0-1	2 (33)	76 (53)	0.42
2	1 (17)	35 (24)	>0.99
≥ 3	3 (50)	29 (20)	0.12
Karnofski			
90 to 100	6 (100)	140 (97)	>0.99
0 to 80	0 (0)	4 (3)	>0.99
Conditioning Regimen			
High dose Busulfan (n; %)	2 (33)	71 (49)	0.68
High dose Treosulfan (n; %)	1 (17)	41 (28)	0.67
High dose TBI-based regimen (n; %)	3 (50)	29 (20)	0.08
GVHD profilaxis			
Use of Sirolimus (n, %)	1 (17)	10 (7)	0.27
Serum bilirubin > 1.5 mg/l (>26 µmol/l) @T0	3 (50)	25 (17)	0.08
Transaminase >2.5 ULN @ T0	0 (0)	9 (6)	>0.99
Median EASIX-T0 (range, IQR)	2,56 (0,86 - 4,45)	1,39 (0,17 - 111,47)	0.19
Median EASIX-T1 (range, IQR)	3,73 (0,88 - 10,49)	2,54 (0,05 - 106,75)	0.64

Table 1 Patients clinical characteristics according to the VOD onset. Categorical variables were summarized as number and percentage and compared using unpaired T-test or Chi-square test, as appropriate. Continuous variables were summarized as median and range and compared using Mann-Whitney U test. All p values ≤ 0.05 were considered statistically significant.

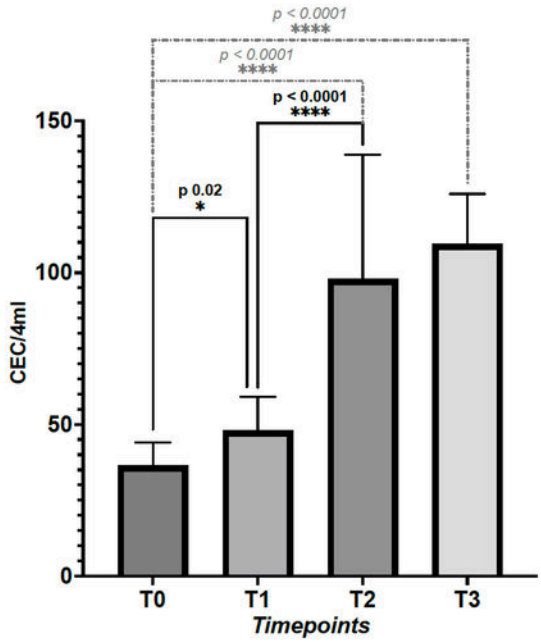

Figure 1: CECs in 4 ml of peripheral blood at different time points. The analysis was performed using the Wilcoxon Test. * = statistical significance with p-value < 0.05; **** = statistical significance with p-value < 0.0001.

Figure 1

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