Incidence and characteristics of chronic GVHD in haploidentical stem-cell transplantation with post-transplantation cyclophosfamide. Experience of the Spanish group of hematopoietic transplantation and cell therapy (GETH-TC)

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Context and Background

Chronic Graft-versus-host-Disesae (cGVHD) is a relevant cause of late morbidity and mortality related to allogenic-stem-cell transplantation in long-term survivors. GVHD prophylaxis using post-transplantation cyclophosphamide (PTCy) has improved haploidentical stem-cell transplantation (haplo-HSCT) outcomes, however data related to characteristics, risk factors or cGVHD outcomes are limited.

In this study, we analyze the incidence, risk factors and disability related to cGVHD in patients undergoing haplo-HSCT PTCy.

Methods

Retrospective multicenter analysis of 389 consecutive patients that underwent haplo-HSCT-PTCy at 7 Spanish transplant-centers from 2007 to 2020. cGVHD diagnosis was made following the NIH criteria and Disability related to cGVHD was defined as as *Fatobene et al* criteria

Results

Patient characteristics' are shown in table 1 and cGVHD characteristics' in table 2.
Median age was 48 years (5-74), 62% were males. AML and HL were the most common indications for transplantation (37%, 22%). 36% received a previous transplant.
The median follow up was 35 months (3-102). Cumulative incidence of aGVHD and aGVHD III-IV at day +180 was 66% and 20%. The 2-year OS was 59%, 2 year PFS 54%, 2 year-GRFS was 45%.
95 patients developed cGVHD, cumulative incidence of cGVHD and cGVHD moderate-severe was 34% and 10% at 3 years. 42 patients required systemic treatment.
In the univariate analysis of risk factors for cGVHD in patients alive on day +100, female donor (p=0.034), female donor and male recipient (p=0.041), DRI low (p=0.026), myeloablative conditioning (p=0-047), previous aGVHD (p=0.014), and the use of radiotherapy in conditioning (p=0.004) were identified. Busulfan conditioning was identified as a protective factor (p=0.036). In multivariate analysis, the presence of previous GVHD (p=0.031) and the protective power of conditioning with busulfan (p=0.036) remains statistically significative. Table 3.

PATIENTS CHARACTERISTICS	N=389
Age at transplant (years), median (range)	48 (5-74)
Donor age (years), median (range)	37 (14-75)
Male, n (%)	242 (62)
Sorror or HCT- CI, %. 0-2, ≥3	251 (64,6), 128 (33)
Diagnosis, n (%)	
AML / MDS / CMML	144 (37) / 37 (10) / 7 (9)
CML / MPS	6 (2) / 12 (3)
HL / NHL	89 (23) / 49 (13)
ALL	34 (9)
Multiple myeloma / Others	5 (1) / 6 (1,6)
Previous treatments, %, >2	134 (34,4)
Previous transplantation, n (%)	
Previous autologous transplantation / Previous allogenic transplantation	105 (27) / 35 (9)
Disease risk index (DRI), %	
Very high/High, Intermediate / Low	7 (1.8) / 47 (12.1), 230 (59.1) / 105 (27)
Donor age (years), median (range)	14 – 75 (37)
Donor-recipient gender match, n (%)	
No mismatch / Female – Male / Male - Female	199 (51,2) / 114 (29,3) / 76 (19,5)
Conditioning regimen, n (%)	
Myeloablative regimen	104 (26,7)
Flu(150mg/m2) +Bu(9,6mg/kg) +Thio(10mg/kg)	54 (51,9)
Flu(150mg/m2) +Bu (9,6 mg/kg) + Cy(29mg/kg)	29 (27,9)
Flu(150mg/m2) +Bu (12,8 mg/kg) + Cy(29mg/kg)	20 (19,2)
Reduced intensity regimen	278 (71,5)
Flu(150mg/m2) +Bu (3,2 mg/kg) + Cy(29mg/kg)	60 (21,6)
Flu(150mg/m2) +Bu (6,4 mg/kg) + Cy(29mg/kg)	167 (60,1)
Flu(150mg/m2) +TBI(2Gy) +Cy(29mg/kg)	23 (8,3)
Flu(150mg/m2) +Bu(6,4mg/kg) +Thio(10mg/kg)	28 (10,1)
	7 (1,8)
Sequential regimen	
GVHD prophylaxis, n(%)	
Tacro + MMF + Cy, CsA + MMF + Cy	250 (64,5), 138 (35,6)
Graft source, n (%)	
Peripheral blood / Bone marrow	312 (80,4) / 76 (19,6)
CD34+ (x106/kg) infused, median (range)	5,3 (0,65-13,68)

Table 1. Patients characteristics

CHRONIC GVHD CHARACTERISTICS	n=95 (%)
cGVHD onset, n (%)	
Progressive / Quiescent /De novo	21 (22) / 50 (53) / 24 (25)
cGVHD overlap, n (%)	24 (25)
Prior late acute GVHD, n (%)	6 (6)
Prior II-IV acute GVHD, n (%)	55 (58)
Prior III-IV acute GVHD, n (%)	14 (15)
NIH severity, n (%). Mild / Moderate / Severe	47 (49) / 25 (26) / 23 (24)
Sites of cGVHD involved, median (range)	1 (1 - 4)
Sites of cGVHD involved, n (%)	
1 or 2 / 3 / >3	77 (81) / 13 (14) / 4 (4)
Sites of cGVHD, n (%)	
Mouth / Skin / Eyes	33 (35) / 43 (45) / 22 (23)
Lung (Bronchiolitis obliterans)	15 (16)
Gastrointestinal tract / Liver	18 (19) / 17 (18)
Joint/fasciae / Genitals	5 (5) / 4 (4)
Triggering factors, n (%). IST reduction / IST suppression / DLI	27 (28) / 14 (15) / 4 (4)
Eosinophils >500/ uL at cGVHD onset, n (%)	7 (7)
Thrombocytopenia, Platelet count <100x10^9/L	26 (28)

Table 1. cGVHD characteristics

RISK FACTORS	UNIVARIATE ANALYSIS			MULTIVARIATE ANALYSIS		
	p	HR	CI 95%	p	HR	CI 95%
Donor sex female	**0.034**	1.547	1.032-2.318	0.835	1.061	0.610-1.844
Male receptor Female donor	**0.041**	1.548	1.018-2.356	0.260	1.394	0.782-2.482
Recipient age ≥ 60 years	**0.015**	0.485	0.270-0.871	**0.044**	0.517	0.272-0.981
DRI low	**0.026**	1.608	1.059-2.441	0.107	1.465	0.921-2.330
Myeloablative conditioning	**0.047**	1.521	1.005-2.301	0.597	1.153	0.680-1.953
Conditioning including radiotherapy	**0.004**	2.413	1.317-4.423	0.331	1.475	0.673-3.230
Conditioning including Busulphan	**0.002**	0.531	0.352-0.799	**0.036**	0.547	0.311-0.962
Previous aGVHD	**0.014**	1.859	1.134-3.047	**0.031**	2.044	1.068-3.911

Table 2. Univariate and Multivariate analysis of risk factors for cGVHD (showing significative results)

cGVHD according to NIH at 3 years, moderate cGVHD showed a higher OS (p=0.054), higher PFS (p=0.004) and lower relapse than the rest of the groups (p=0.035) Figure 1. Receiving one line of treatment (p=0.043) and use of bone marrow were the only risk factors identified for this patients.

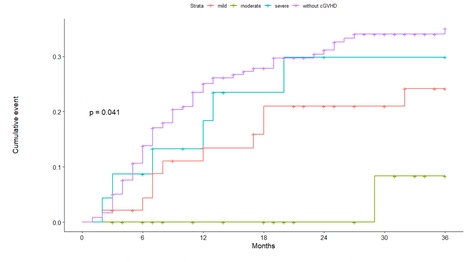


Figure 1. Relapse stratified by cGVHD NIH

Conclusions

Haplo-HPT with Cy-post shows a low, but not negligible incidence of cGVHD and its use represents an alternative for some patients.
The development of moderate cGVHD is a protective factor in this transplant modality. The characterization of predictive factors of this subgroup is relevant given the results.

References

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