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ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION IN THE ELDERLY. PREDICTING THE RISK FOR NON RELAPSE MORTALITY

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Abstract We have retrospectively reviewed 137 medical records of patients older than 50 years receiving an allogeneic hematopoietic stem cell transplantation (HSCT) between January 1997 and July 2013. Median follow up was 1.3 years. Sex, age, diagnosis, disease stage, comorbidities (according to HCT-CI score), type of donor, histocompatibility, conditioning regimen and graft-versus-host disease (GVHD) prophylaxis were evaluated. The incidence and severity of acute and chronic GVHD, overall survival (OS), disease free survival (DFS), non-relapse mortality (NRM) and relapse were investigated according those variables. Acute GVHD incidence was 41% (7.3% GIII-IV). Patients with acute myeloid leukemia had lesser aGVH GII-IV (14% vs. 35%, $p < 0.01$) comparing to the entire population. Extensive cGVHD incidence was 9.4%. Global OS 1-3 years was 44-20%, DFS 33-20%, relapse 35-41% and NRM 36-43% respectively. The presence of comorbidities showed a significant increase in NRM (CT-CI 0 vs. 1 vs $\geq$ 2: 1-3 years 17-24% vs. 40-46% vs. 45-67%, $p = 0.001$, MA HR 2.03, CI 95% 1.02-5.29), as well as cyclosporine vs. tacrolimus (1-3 years 47-53% vs. 25-36%, $p = 0.01$). Tacrolimus patients had higher 1-3 years OS (49-25% vs. 31-13%, $p = 0.01$) and DFS (41-26% vs. 20-11%, $p < 0.01$). Age, type of donor and myeloablative conditioning showed no significant differences in any outcome. Allogeneic HSCT is a valid therapeutic option for older patients in Argentina. The main risk factor for a significantly increased NRM and a trend to inferior OS was the number of comorbidities. Age was not a factor for a worse result. The other factor having a significant effect in better outcome was tacrolimus administration.

Key words: elderly, hematopoietic stem cells transplantation, co-morbidities

Resumen ***Trasplante alogénico de precursores hematopoyéticos en pacientes mayores de 50 años. Riesgo de mortalidad libre de enfermedad.*** Se efectuó un análisis retrospectivo de 137 historias clínicas de pacientes mayores de 50 años que recibieron un trasplante alogénico de precursores hematopoyéticos (TAPH). Se evaluaron las siguientes características: sexo, edad, enfermedad, estadio, comorbilidades (según el HCT-CI), donante, acondicionamiento e inmunosupresión. Se analizó la incidencia de enfermedad injerto vs. huésped aguda (aEICH) y crónica (cEICH), supervivencia global (SG), supervivencia libre de enfermedad (SLE), recaída y mortalidad libre de enfermedad (MLE). Los trasplantes fueron realizados entre 1997-2013, mediana de seguimiento 1.3 años. La incidencia de aEICH fue de 41% (7.3% GIII-IV). Los pacientes con leucemia mieloide aguda presentaron menor incidencia de EICHa GII-IV (14% vs. 34%, $p < 0.01$). La incidencia de EICHc extenso fue de 9.4%. La SG a 1-3 años fue 44-20%, SLE 33-20%, recaída 35-41% y la MLE 36-43%. Los pacientes con comorbilidades tuvieron un aumento significativo de la MLE (HCT-CI 0 vs. 1 vs. $\geq$2: 1-3 años 17-24% vs. 40-46% vs. 45-67%, $p = 0.001$, AMV HR 2.03, IC 95% 1.02-5.29), al igual que el uso de ciclosporina vs. tacrolimus (1-3 años 47-53% vs. 25-36%, $p = 0.01$). Los pacientes que recibieron tacrolimus tuvieron una mayor SG (1-3 años 49-25% vs. 31-13%, $p = 0.01$) y SLE (1-3 años 41-26% vs. 20-11%, $p < 0.01$). La edad, tipo de donante y acondicionamiento no resultaron significativos para ningún evento.
El TAPH es una herramienta terapéutica válida en pacientes mayores. Los factores pronósticos que inciden mayormente en el trasplante son las comorbilidades y no la edad. El otro factor que demostró un efecto significativo fue el uso de tacrolimus.

Palabras clave: pacientes mayores, trasplante hematopoyético de células madre, comorbilidades

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Glossary

HSCT: Hematopoietic Stem Cell Transplant
HCT-CI: Hematopoietic cell transplant-Comorbidity Index
GVHD: graft-vs-host disease
aGVHD: acute GVHD
cGVHD: chronic GVHD
OS: overall survival
DFS: disease free survival
NRM: non relapse mortality
MA: multivariate analysis
FK: tacrolimus

Allogeneic hematopoietic stem cell transplantation (HSCT) is an effective therapy for several hematological malignancies. HSCT has the potential to cure some diseases otherwise incurable with conventional treatments[1-5]. Initially, allogeneic HSCT was offered to young patients due to the high morbidity and mortality associated with the procedure[6-8]; however the majority of the hematological malignancies have an incidence peak at advanced age[9-14]. This group of patients is especially vulnerable for the allogeneic HSCT toxicities, not only because of age, but also because of comorbidities present in this population. During the last decade less toxic conditioning were introduced in the transplant setting. Reduced intensity conditioning has allowed older patients to undergo HSCT[1, 15-20].

Based on comorbidities, Sorror et al validated the hematopoietic co-morbidity index (HCT-CI) predicting the risk for non-relapse mortality and overall survival before HSCT[21]. This score is used in the majority of HSCT publications at present[22-24]. We described the experience with allo-HSCT in 137 patients older than 50 years in nine institutions in Argentina. We aimed to study the value of the HCT-CI score in our population, as well as evaluate other risk factors associated with morbidity and mortality. Preliminary data were presented at the *Sociedad Argentina de Hematología* meeting in 2013.

Materials and Methods

We retrospectively reviewed 137 consecutive medical records of patients older than 50 years receiving an allogeneic HSCT in our institutions. The following characteristics were evaluated: sex, age, diagnosis, stage at transplant, co-morbidities (according to the HCT-CI score), type of donor, histocompatibility, conditioning and immunosuppressive agents. Early stage at transplant was considered for acute myeloid leukemia or acute lymphoblastic leukemia if patients were in first complete remission, for chronic myeloid leukemia in chronic phase, and myelodisplastic syndrome in complete remission, otherwise was considered late stage.

For the statistical analysis SPSS (17.0) and R (2.9.1) were used. The incidence and severity of acute Graft-vs.-Host disease (aGVHD) was compared with Chi Square test. Overall survival (OS) and disease free survival (DFS) were analyzed with Kaplan Meier method. For chronic GVHD (cGVHD), relapse and non-relapse mortality (NRM) it was employed a cumulative incidence analysis (NRM was the competing event for relapse, for NRM the competing event was relapse and for cGVHD were death/relapse). For multivariate analysis variables that in univariate analysis had a $p \leq 0.2$ were included. Cox regression model was utilized for time dependant outcomes and logistic regression for dichotomic variables, considering significant a $p < 0.05$.

TABLE 1.– *Cohorts characteristics*

		N (%)
Patients, age median 55 years (y)	≥ 60 y	24 (17.5)
	< 60 y	113 (82.5)
Donors, age	< 50 y	47 (34)
	≥ 50 y	57 (42)
	Missing	33
Patients, sex	Male	90 (66)
	Female	47 (34)
Donors, sex	Male	77 (56)
	Female	54 (39)
	Missing	6
HCT-CI score	0	51 (37)
	1	37 (27)
	≥2	35 (25)
	Missing	14
Disease	Acute myeloid leukaemia	50 (36)
	Myelodisplastic syndrome	40 (29)
	Myeloproliferative neoplasm	24 (17)
	Lymphoproliferative disease	10 (7.3)
	Other malignant	12 (8.7)
Disease status	Early	45 (33)
	Late	92 (67)
Conditioning	Myeloablative	33 (24)
	Reduced intensity	104 (76)
Conditioning II	Fludarabine-melphalan	34 (24)
	Fludarabine-busulfan	49 (36)
	Fludarabine-TBI	11 (8)
	Busulfan-cyclophosphamide	25 (18)
	Others	18 (13)
Donor	Sibling	113 (83)
	Unrelated	24 (17)
Source	PBSC	117 (85)
	Bone marrow	19 (33)
Immunosupression	Tacrolimus based	93 (68)
	Cyclosporine based	44 (32)

HCT-CI: hematopoietic cell transplant-comorbidity index, TBI = total body irradiation; PBSC = peripheral blood stem cells

Results

Transplants were performed between January 1997 and July 2013, and the median follow up was 1.3 years. Patients' characteristics are listed in Table 1. Eighty two percent of the patients (113) were younger than 60 years, 66% (90) were male. Nearly two third of the patients (63%) had HCT-CI score 1 or more. Acute myeloid leukaemia was diagnosed in 36%, myelodisplastic syndrome in 29%, of these, 67% were in late stage. Seventy six percent received a reduced intensity conditioning regimen, mainly fludarabine-based, 82% received a transplant from

TABLE 2.– *Multivariate analysis of disease free survival*

	p value	Odds Ratio	95% CI	
			Lower	Upper
Patients younger than 60 years	0.52	1.24	0.63	2.47
Acute leukaemia	0.05	1.59	0.98	2.55
HCT-CI ≥1	0.21	1.38	0.83	2.29
Fludarabine-busulfan	0.97	1.00	0.60	1,66
HLA mismatched	0.81	1.10	0.49	2.46
Sibling donor	0.09	0.54	0.27	1.10
Tacrolimus based GVHD prophylaxis	0.03	0.54	0.31	0.95

HCT-CI: hematopoietic cell transplant-comorbidity index

a sibling donor and 68% received tacrolimus-containing GVHD prophylaxis.

Acute GVHD incidence was 41% (19% were grades II and 7.3% grades III-IV). The only variable associated with aGVHD clinically significant (grades II-IV) was the diagnosis of acute myeloid leukemia, being protective (14% vs. 34%, p < 0.01) and also significant in multivariate analysis (HR 0.29; 95% CI 0.12-0.72). Chronic GVHD incidence was 25%, extensive in 9.4% and the only risk factor associated with this outcome was myeloproliferative neoplasm (1-3 years 40-40% vs. 12-20%, p = < 0.01).

One and three years relapse incidence was 35% and 41%, and NRM was 36 and 43% respectively. Patients with comorbidities showed a significant increase in NRM (HCT-CI 0 vs. 1 vs. ≥2, 1-3 years 17-24%, 40-46% and 45-67%, p < 0.01, figure 1.A; significant in multivariate analysis, for HCT-CI 0 vs. ≥ 1, HR 2.3, 95% CI 1.02-5.29, Table 2); as well as male patients (1-3 years 36-47% vs. 23-27%, p = 0.01), diagnosis of myeloproliferative neoplasm (1-3 years 43-65% vs. 29-34%, p = 0.02) and cyclosporine containing GVHD prophylaxis vs. tacrolimus (1-3 years 47-53% vs. 25-36%, p < 0.01) (figure 1.B). Regarding relapse incidence, acute myeloid leukemia patients experienced a higher rate (1-3 years 53-56% vs. 27-29%, p < 0.01) compared to other diagnosis.

Global OS at 1 and 3 years was 44 and 20% and DFS was 33 and 20%. Patients receiving tacrolimus vs. cyclosporine based prophylaxis had higher OS (1-3 years 50-25% vs. 31-13%, p = 0.01) (figure 2.A) and DFS (1-3 year 41-27% vs. 17-8%, p < 0.01, figure 2.B); significant in multivariate analysis (HR 0.54, 95% CI 0.31-0.95 (Table 2). Similarly, patients without comorbidities (HCT-CI 0 vs. ≥1) had a trend towards a higher OS (1-3 years 54-30% vs. 38-17%, p=0.05) as well as a higher DFS (1-3 years 42-30% vs. 30-16%, p =0.06).

Patients older than 60 years showed no significant differences in terms of NRM (1-3 years 17-23 vs. 34-43%, p = 0.08) and DFS (1-3 years 46-35% vs. 31-18%, p = 0.1). Interestingly, regarding OS, this group experienced higher OS (1-3 years 59-45% vs. 41-18%, p = 0.02), not significant in multivariate analysis. Similarly, type and age of donor, use of myeloablative conditioning regimen, use of in vivo T cell depletion and stem cell source showed no significant difference in any outcome analyzed.

Discussion

In this analysis we described our experience with HSCT in patients older than 50 years, showing outcomes comparable to other centres[18, 25-27]. Forty percent of the patients had aGVHD, 26% had clinical significant forms and only 7% had severe forms. NRM incidence was around 36% at 1 year and less than 45% at 3 years; and long term DFS and OS were around 20%. In a similar experience, Alyea et al, describe an incidence of clinically significant aGVHD of 27-29% and 17-20% of severe forms depending on conditioning and type of donors. In terms of time dependant variables, two years OS was 39-29%, DFS 27-25% and a NRM cumulative incidence of 32-50% for non-myeloablative and myeloablative regimes respectively[17].

For aGVHD, the only factor associated with significant differences was the diagnosis of acute myeloid leukemia,

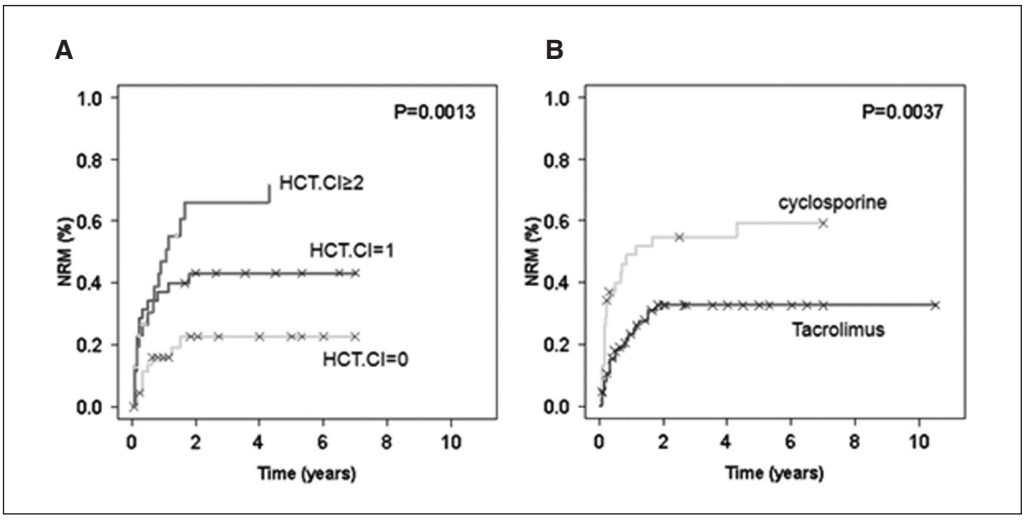

Fig. 1.– Non relapse mortality (NRM) curves. A: according to Hematopoietic Cell Transplant-Comorbidity Index score (HCT-CI), B: according to graft-vs-host disease (GVHD) prophylaxis: cyclosporine (CSA) vs. tacrolimus.

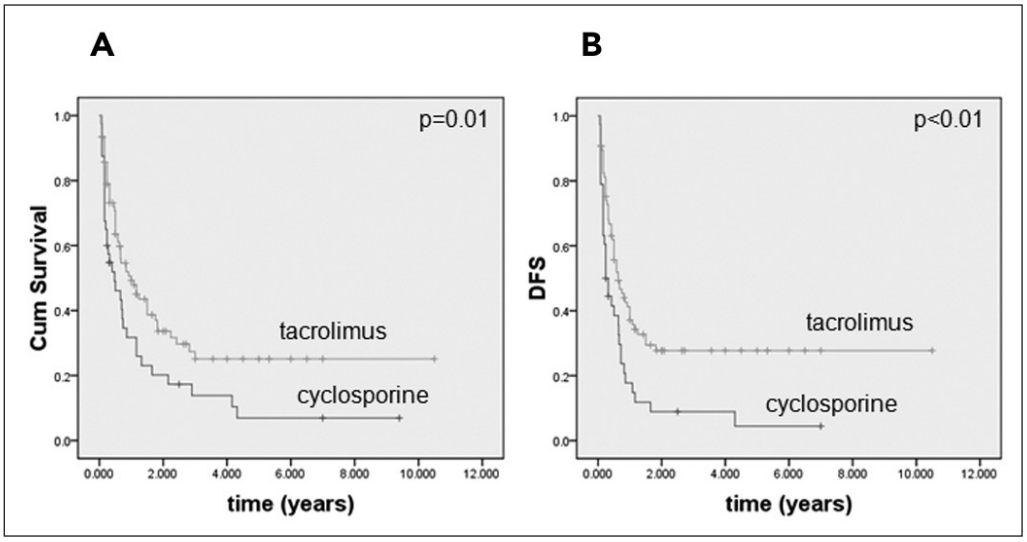

Fig. 2.– Overall survival (OS). A: and disease free survival (DFS), B: according to GVHD prophylaxis: cyclosporine vs. tacrolimus

showing a protective effect. Alousi et al described an increase of incidence and severity of aGVHD in unrelated donors, peripheral blood stem cell source and cyclosporine based prophylaxis[8]. Probably due to the low numbers of unrelated donor and HLA mismatch donors in our cohort, these variables did not show a significant increase in aGVHD incidence. For cGVHD the only factor associated was the diagnosis of myeloproliferative neoplasm. As for aGVHD, Alousi et al. described similar risk factors (unrelated donor, peripheral blood stem cell source and T-cell deplete graft) associated with cGVHD.

Comorbidities assessed by HCT-CI score were the most important predicting factor for NRM. Similarly to Sorror et al. experience, validated by Takasaki in a population similar to ours[28], intermediate HCT-CI score patients (1 or 2) have a non-relapse mortality (NRM) rate of 21% at 2 years and high-risk patients (HCT-CI 3 or more) have a NRM rate of 40% at 2 years[21]. In our population, transplant related toxicities increase with the number of comorbidities. Patients with HCT-CI 0 had 20% NRM rate at 1 year, compared to 40 and 45% with 1 or $\geq$ 2 HCT-CI score respectively. These variables had a direct influence on OS and DFS, although not significant probably due a low number of patients.

We observed that tacrolimus-containing regimens compared to those with cyclosporine had a better outcome. This approach showed a significantly higher long term (3 years) OS (25% vs. 13%) and DFS (27% vs. 8%) based

on a lower 3-year NRM (36% vs. 53%). Several authors evaluated this comparison with no conclusive results with the exception of a Japanese study describing a better OS due to low TRM for the tacrolimus-based approach in unrelated donor HSCT cohort, but not in the sibling donor cohort[29-35]. The same problem was addressed by Ram et al in a meta-analysis comparing both treatments, observing no differences in terms of survival outcomes, aGVHD incidence and severity was the only variable influenced by the type of prophylaxis employed[36].

Interestingly, patients older than 60 years had higher OS, although not significant in multivariate analysis, compared to younger patients. This was probably due to a better patient selection: only 13% of the patients had HCT-CI higher than 1, 12% received a transplant from an unrelated donor as well as a myeloablative conditioning regimen and 96% received tacrolimus-based GVHD prophylaxis.

In conclusion, in this experience we demonstrate that allogeneic HSCT is an option for older patients in Argentina, even beyond the age of 60 years. The best candidates would be patients with one or no comorbidities, receiving tacrolimus-based GVHD prophylaxis and a reduce intensity conditioning regimen.

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Conflict of interests: None to declare

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Fortis imaginatio generat casum [Une imagination forte produit l´évènement].

Je suis de ceux qui ressentent intensément la force de l´imagination. Chacun en est heurté, mais aucuns en sont renversés.[…]. Je vivrais de la seule présence de personnes saines et gaies. La vue des angoisses d´autrui m´angoisse physiquement : et mes sens ont souvent perçu le sentiment d'un tiers. Un tousseur continuel irrite mon poumon et mon gossier. Je répugne davantage à *visiter les malades, auxquels le devoir me lie, que ceux auxquels j´accorde moins d´attention, et que je considère moins. Je saisis le mal, que j´étudie, et le couche en moi.*

[Una imaginación fuerte produce el acontecimiento]

Soy de los que sienten intensamente la fuerza de la imaginación. Todo el mundo es golpeado, pero algunos son derribados por ella. […] Viviría con la sola presencia de personas sanas y alegres. La vista de las angustias del otro me angustia físicamente, y mis sentidos han percibido a menudo el sentimiento de un tercero. Un continuo tosedor irrita mi pulmón y mi garganta. Me desagrada más visitar a los enfermos, a quienes el deber me ata, que a aquellos a los que concedo menos atención, y a los que considero menos. Tomo el dolor, que estudio, y lo acojo en mí.

Les Essais de Michel de Montaigne. Livre I, Chapitre XX : De la force de l´imagination.
Paris: Le libre de poche, 2001, p 146