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ORIGINAL ARTICLE

The Latin American experience of allografting patients with severe aplastic anaemia: real-world data on the impact of stem cell source and ATG administration in HLA-identical sibling transplants

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We studied 298 patients with severe aplastic anaemia (SAA) allografted in four Latin American countries. The source of cells was bone marrow (BM) in 94 patients and PBSCs in 204 patients. Engraftment failed in 8.1% of recipients with no difference between BM and PBSCs ($P = 0.08$). Incidence of acute GvHD (aGvHD) for BM and PBSCs was 30% vs 32% ($P = 0.18$), and for grades III–IV was 2.6% vs 11.6% ($P = 0.01$). Chronic GvHD (cGvHD) between BM and PBSCs was 37% vs 59% ($P = 0.002$) and extensive 5% vs 23.6% ($P = 0.01$). OS was 74% vs 76% for BM vs PBSCs ($P = 0.95$). Event-free survival was superior in patients conditioned with anti-thymocyte globulin (ATG)-based regimens compared with other regimens (79% vs 61%, $P = 0.001$) as excessive secondary graft failure was seen with other regimens (10% vs 26%, $P = 0.005$) respectively. In multivariate analysis, aGvHD II–IV (hazard ratio (HR) 2.50, confidence interval (CI) 1.1–5.6, $P = 0.02$) and aGvHD III–IV (HR 8.3 CI 3.4–20.2, $P < 0.001$) proved to be independent negative predictors of survival. In conclusion, BM as a source of cells and ATG-based regimens should be standard because of higher GvHD incidence with PBSCs, although the latter combining with ATG in the conditioning regimen could be an option in selected high-risk patients.

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INTRODUCTION

Allogeneic haematopoietic stem cell transplantation is considered the treatment of choice with curative potential for severe aplastic anaemia (SAA).[1] Bone marrow (BM) is regarded as the best source of stem cells in HLA-matched related and unrelated transplantation for SAA, as a survival advantage and less GvHD have been found in large retrospective studies that compare BM with PBSCs.[2,3] In high-income countries, BM is the main source of stem cells, whereas in countries with limited resources, where haematology teams face referral of patients in advanced stages, heavy pretreatment and HLA allo-sensitization due to multiple transfusions, the use of PBSCs is frequent.[4,5] Regarding conditioning regimens, anti-thymocyte globulin (ATG)-based regimens are the standard of care, but because of financial or bureaucratic constraints in countries with limited government-supported health-care systems, regimens without ATG are also frequently used. The objective of this study was to analyse the long-term results of a large, multicentre cohort of patients with SAA allografted in four Latin American countries (LAc), the outcomes with different conditioning regimens and the source of stem cells. Results are compared with those of large SAA studies and, as a final aim, we provide an overall perspective of the experience of allografting SAA patients in our region.

MATERIALS AND METHODS

We included 298 patients with acquired SAA and a first transplant diagnosed between 1990 and 2014 who received an allogeneic haematopoietic stem cell transplant using BM or PBSC at 19 centres in four LAc. We analysed the overall survival (OS) of the entire cohort and then split it into two groups: the first included 94 BM-allografted patients

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from Argentinian centres, whereas the second included 204 PBSC-transplanted patients from Mexico, Peru and Colombia. All cases were submitted to an institutional review board and transplant committee for approval; written informed consent was obtained from patients and donors. The choice of conditioning regimens was made according to each institution's guidelines and were grouped into two different categories: (1) the ATG-based regimens included cyclophosphamide (CY)+ATG (equine or rabbit-derived), CY+ATG and fludarabine (CY+ATG+FLU) and CY+ATG+TBI; (2) other regimens that were FLU based included CY+FLU, CY+FLU +alemtuzumab (CY+FLU+ALEM), CY+FLU+busulfan (CY+FLU+BU) and FLU +BU; CY-based regimens included CY alone, CY+TBI and BU+CY. Doses of regimens are specified in Supplementary Table 1. All regimens were compared against ATG-based regimens. All donors were full HLA-identical siblings. PBSCs were collected after donor stimulation with G-CSF at 10–15 μg/kg. Patients were classified as multi-transfused if they had received $\geqslant 20$ units of packed red cell or platelet concentrates. Post-transplant (PT) neutrophil and platelet recovery was defined as three consecutive days with an absolute count $\geqslant 500 \times 10^9$/L and $\geqslant 20 \times 10^9$/L, respectively, unsupported by transfusions. Primary outcomes were OS from transplant until the occurrence of an event (death) and event-free survival (EFS) from the day of transplant to the occurrence of death or relapse. Secondary outcomes included incidence of GvHD, primary and secondary graft failure (GF) and the effect of conditioning regimen on survival.

Each statistics department of each centre assessed the quality of data and several authors were involved in internal data audits. Comparisons of categorical values were carried out using the χ^2 test and the Mann–Whitney test for continuous variables. OS and EFS were calculated using the Kaplan–Meier method and outcome variables were compared in subgroups of patients by the log-rank test. Incidence of grade II–IV and III–IV acute GvHD (aGvHD) and limited or extensive chronic GvHD (cGvHD) were reported using standardized criteria.[6–8] GF, day 100 mortality, GvHD and relapse were summarized using cumulative incidences with 95% confidence intervals (CIs) taking into account death as a competing risk and compared using Gray's test. Univariate Cox regression analysis was performed to assess the effect of treatment, source of stem cells and GvHD as a time-dependent covariate, with two-sided *P*-values of $\leqslant 0.05$ considered as statistically significant; pertinent variables were used to fit a multivariate analysis. Data were analysed using SPSS version 22 (SPSS Inc., Chicago, IL, USA) and cumulative incidence with competing risks and Gray's test with R commander software packages 2.2–3 (R Development Core Team, Vienna, Austria) and EZR by Y Kanda in the Division of Hematology of Saitama Medical Center.[9]

Table 1. Baseline clinical characteristics of patients and conditioning regimens used

Source	*Bone marrow* (n = *94*)	*Peripheral blood* (n = *204*)	P-*value*
Age in years, median (range)	19 (2–52)	29 (2–65)	< 0.001
< 21 Years, *n* (%)	58 (61)	64 (31.4)	< 0.001
Sex male, n (%)	63 (67)	128 (62.7)	0.51
Days from diagnosis to transplant, median (range)[a]	86.5 (21–4350)	202.5 (21–4436)	< 0.001
ATG-based regimens, *n* (%)	74 (78.7)	145 (71.1)	0.204
Other regimens, *n* (%)	20 (21.3)	59 (28.9)	
Year of transplant, n *(%)*			
1990–1995	2 (2.1)	3 (1.5)	
1996–2000	28 (29.8)	16 (7.8)	
2001–2005	17 (18.1)	59 (28.9)	
2006–2010	27 (28.7)	80 (39.2)	
2011–2015	20 (21.3)	46 (22.5)	
Number of patients included by country, n *(%)*			
Mexico		62 (30.4)	
Peru		69 (33.8)	
Colombia		73 (35.8)	
Argentina	94 (100)		
Follow-up of survivors, median (range) in days	2454 (202–7645)	2106 (76–8289)	

Abbreviation: ATG = anti-thymocyte globulin. [a]Two patients received ATG and androgens with response for more than 10 years and then were allografted in relapse.

RESULTS

Overall, 298 patients received an allogeneic BM ($n = 94$) or PBSC ($n = 204$) transplant. Characteristics of patients and conditioning regimens used are shown in Table 1. Data on previous treatment were available for 173 patients; 81 (27%) did not receive any kind of immunosuppressive therapy; 50 (16.7%) were treated with ATG +cyclosporine A (CsA) and 42 (14%) with androgens, CsA, steroids or combinations of these medications. Data for 125 patients (42%) were not reported.

Of the 219 (73.5%) patients treated with ATG-based regimens, 61 (27.9%) received equine ATG (Atgam, Pfizer, New York, NY, USA) and 158 (72.1%) rabbit-derived ATG (Thymoglobulin, Sanofi, Gentilly, France). Most patients (61%, $n = 183$) were treated during 2001–2010, when the use of PBSCs was more frequent in LAc because of the ease and lower cost of collection. All patients received GvHD prophylaxis and regimens were heterogeneous: 80% ($n = 239$) received methotrexate at 10–15 mg/m^2 in three to four doses on days +1, +3, +6 and +11 as well as CsA at 3–5 mg/kg targeting a serum concentration of 250–350 ng/mL; 9.4% ($n = 28$) received CsA 3–5 mg/kg+mycophenolate mofetil 2 g/day from days 1 to 28; 7.7% ($n = 23$) received CsA alone at 3–5 mg/kg; and 2.7% ($n = 8$) received CsA 3–5 mg/kg+methylprednisolone at 0.5–2 mg/kg/day for at least 30 days. All patients received antibacterial, antifungal and antiviral prophylaxis during the phase of aplasia and regimens were heterogeneous but mainly consisted of levofloxacin/ciprofloxacin, fluconazole and acyclovir. Co-trimoxazole was started on day − 6, discontinued 1 day before stem cell infusion and restarted after neutrophil recovery. The median dose of CD34+ cells administered was 3.96×10^6 (range 0.40–43.6)/kg of recipient body weight.

Haematopoietic recovery and primary GF

The cumulative rate of engraftment for BM and PBSCs was 88% and 94% ($P = 0.08$). G-CSF was not routinely used PT. Median neutrophil recovery was documented at day 19 (range 9–42) and 11 (range 7–35) ($P < 0.001$) for BM and PBSCs, respectively. For platelets, median recovery was at day 24 (range 12–104) and day 12 (range 7–28) ($P < 0.001$) for BM and PBSCs, respectively. Twenty-one patients died before engraftment, 17 because of infections; in 4 no specific cause was reported. Comparing patients conditioned with ATG-based regimens (74%, $n = 219$) against those receiving other regimens (26%, $n = 79$), more patients failed to engraft with the latter (6% vs 14%, $P = 0.01$). We could not obtain the transfusion history of the BM-allografted group, but 58% of patients in the PBSC group were considered multi-transfused and no relationship between receiving multiple transfusions and primary GF was found ($P = 0.78$).

Secondary graft failure

In total, 8% of patients ($n = 22$) lost their grafts, and more patients who did so received regimens different from ATG-based regimens (10% vs 26%) ($P = 0.005$). BM vs PBSC graft loss was 18% vs 13% ($P = 0.75$), respectively. Patients in the PBSC group considered heavily transfused (58%) were at no higher risk of secondary GF ($P = 0.60$).

GvHD

The cumulative incidence of acute GvHD grades II–IV (aGvHD) and cGvHD for BM and PBSCs was 30% vs 32% ($P = 0.189$) and 37% vs 59% ($P = 0.002$), respectively. Regarding aGvHD grades III–IV, incidence was lower with BM (2.6%) compared with PBSCs (11.6%) ($P = 0.010$); the same holds true for extensive cGvHD with BM (5%) compared with PBSCs (23.6%) ($P = 0.005$; Table 2). Taking into consideration conditioning regimens, the incidence of aGvHD grades II–IV was 30% for ATG-based regimens and 38% for other regimens ($P = 0.033$). For cGvHD and ATG-based regimens, incidence was 50% vs 54% for other regimens ($P = 0.11$) and no difference in extensive cGvHD between ATG-based regimens and other regimens (18.6% vs 11.1%, $P = 0.80$) was documented.

Age was not associated with the development of GvHD. The incidence of aGvHD grades II–IV ($P = 0.61$) and grades III–IV ($P = 0.89$) was not statistically different in patients older than 21 years; the same was true for cGvHD ($P = 0.39$) and extensive cGvHD ($P = 0.49$).

Secondary malignancies

Seven patients (2.2%) were diagnosed with secondary malignancies, after a median of 1099 days PT (30–2780). Four patients developed AML, one was diagnosed with hairy cell leukaemia, and two patients developed solid malignancies (ovarian and tongue cancer).

Causes of mortality

Seventy-nine (26.5%) patients died with a median follow-up of 215 days (4–4423 days). The most common causes of death were infection in 26 patients (33%), GvHD in 21 (27%), graft failure <100 days PT in 17 (20%) and >100 PT in 6 (7%), secondary neoplasia in 4 (5%), and other causes in 5 patients (6%). Infectious agents identified included CMV, Aspergillus, H1N1 and mucormycosis. Mortality within the first 100 days PT for BM and PBSCS was 6% vs 8% ($P = 0.42$) and not statistically different between ATG-based regimens (8%) and all other regimens (15%) ($P = 0.07$). Overall risk of death between ATG-based regimens and all other regimens was statistically significant ($P = 0.005$, hazard ratio (HR) 1.92, CI 1.2–3.02).

OS and EFS

The median OS of the entire cohort was 76% at 5-year follow-up and 68% at 10-year PT (Figure 1a). Median follow-up of surviving patients was 2140 days (range 76–8289). Survival at 5-year PT was 74% vs 76% ($P = 0.95$) and EFS 70% vs 73% ($P = 0.64$) for BM and PBSCS, respectively (Figures 1b and c). Twenty-one patients died 5 years after transplant, mostly because of infections related to cGvHD and its treatment and also from secondary malignancies.

OS comparison between ATG-based regimens and all other regimens was 80% vs 65% at 5 years ($P = 0.004$; Figure 1d). Regarding EFS at 5 years, ATG-based regimens (79%) were superior to all other regimens (61%) ($P = 0.001$). OS of patients $\geqslant 21$ years old (38%, $n = 122$) was 76% and analysing those who received BM or PBSCs was 73% vs 78%, ($P = 0.61$) at 5-year PT. Patients $\geqslant 21$ years old (62%, $n = 176$) had an OS of 75% at 5 years, similar to younger patients ($P = 0.52$); on the other hand, OS for patients younger or older than 40 years was 80% vs 75% ($P = 0.91$), respectively. The median time from diagnosis to transplant was 157 days (range 21–4436). Transplantation beyond this time was not a predictor of death ($P = 0.71$; Table 3).

Multivariate analysis

Pertinent variables were included in a multivariate analysis. Presence of aGvHD II–IV (HR 2.50, CI 1.1–5.6, $P = 0.02$) and aGvHD III–IV (HR 8.3, CI 3.4–20.2, $P < 0.001$), proved to be independent negative predictors of survival (Table 4).

DISCUSSION

We report the results of a large cohort of patients allografted in four LAc and confirm the positive impact of ATG in the conditioning regimen as well as the increased risk of GvHD related to the use of PBSCs. Currently, BM-derived cells and CY in combination with ATG is the standard of care for SAA in the setting of transplantation from HLA-identical sibling donors. We could not detect a significant difference in OS between BM and PBSCs; however, larger and more robust studies have supported these concepts.[2,3,10] Acknowledging the aforementioned studies, BM as a source of stem cells should be the standard of care, and PBSC+ATG-based regimens may have a role in selected cases, such as heavily transfused patients, or in the case of a second transplant once BM has failed. Recently, a study by Kumar *et al.*[11] described the same phenomena; they found that OS was higher with BM in high-income countries, whereas in upper-middle income countries and low-income countries there was no survival difference between BM and PBSCs, suggesting that PBSCs may be an alternative to BM in patients living in countries with limited resources at high risk of graft failure because of multiple transfusions preceding allografting, among other reasons.

The cohort of BM allografted patients had a survival of 74%, lower than that reported by WPSAA-EMBT (84%)[2] and CIBMTR (85%).[3] There are several explanations for these differences in survival; for instance, 20 patients (21%) in this group did not receive ATG, and 12% suffered primary failure resulting in the majority of cases in death and had a median of an 8- and 12-day delay in neutrophil and platelet recovery, respectively, exposing them to infectious and bleeding complications. Regarding patients allografted with PBSCs, OS in our study was 76%, comparable to 68% reported by WPSAA-EBMT.[2] In this setting, a

Table 2. Comparison of cumulative incidence of graft failure, day 100 mortality and GvHD according to the source of stem cells

	Bone marrow	*PBSCT*	P-*value*
Patient number	94	204	
Primary graft failure	13% CI (6.4–19.9)	6% CI (3.3–9.9)	0.08
Day 100 mortality	6.3% CI (1.3–11.2)	7.8% CI (4.0–11.4)	0.95
aGvHD grades II–IV	30% CI (16.8–44.3)	32% CI (20.2–43.7)	0.18
aGvHD grades III–IV	2.6% CI (0.5–8.3)	11.6% CI (7.4–16.7)	0.01
Chronic GvHD	37% CI (20–55)	59% CI (38.3–74.8)	0.002
Extensive cGvHD	5% CI (0.8–15.1)	23.6% CI (10.6–39.4)	0.005
Secondary graft failure	18% CI (5.6–37)	13% CI (6.5–20.7)	0.75

Abbreviations: aGvHD = acute GvHD; CI = confidence interval; cGvHD = chronic GvHD.

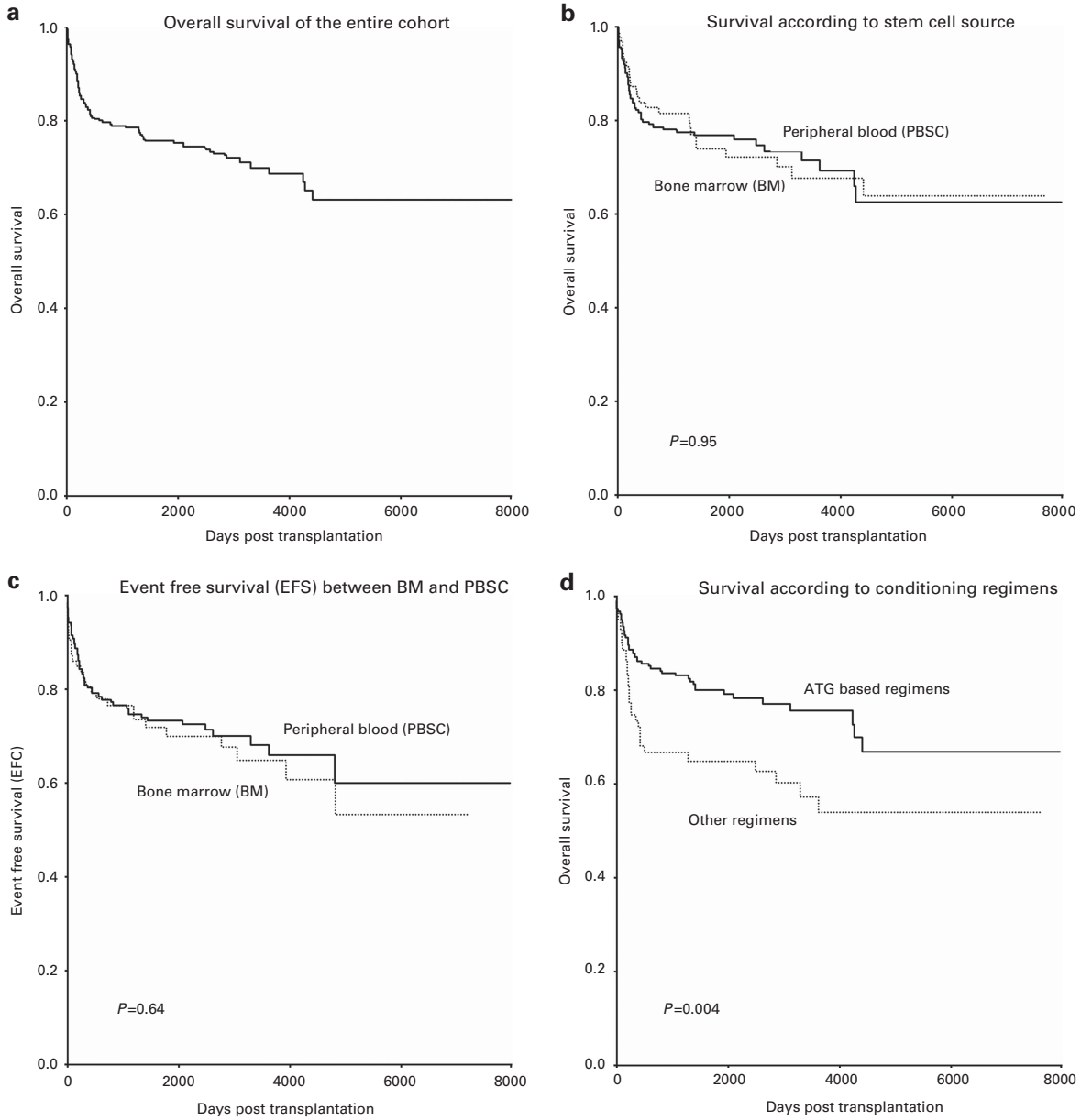

Figure 1. Outcomes. (**a**) overall survival of the entire cohort, (**b**) survival according to the stem cell source, (**c**) EFS between BM and PBSCs and (**d**) survival according to conditioning regimens.

large proportion of PBSC allografted patients (72%) received ATG during conditioning and, even with an increased incidence of GvHD, achieved prolonged survival. Our data indicate no difference in the cumulative rate of engraftment between BM and PBSCs (87% vs 94%, $P = 0.08$), although there was a tendency to have less primary graft failure with PBSCs. These figures might be related to the fact that the dose of CD3+ lymphocytes in the PBSC grafts is larger, yielding faster haematologic recovery; other studies have reported the same phenomena.[2,10]

The upper age limit for HLA-matched sibling transplant as first-line therapy for SAA is different in transplant centres around the world, but it is considered to be 40 years.[12,13] In this scenario, 17% ($n = 52$) of our patients were >40 years old and 75% survived beyond 5 years. In some LAc, such as Mexico, allografting is frequently offered as first-line treatment for many patients >40 years old who have an HLA-related donor and who are reasonably fit when undergoing the procedure.[14,15] This selection criterion may have biased a better result for OS than has been reported for the general population in this age range and may explain the lack of difference in OS in this group when compared with younger patients.

We had incomplete data related to transfusion history in the BM group, but in the PBSC group, as many as 58% of patients were considered heavily transfused and most likely HLA allo-sensitized. This factor, however, was not associated with increments in graft rejection, relapse or in incidence of GvHD. In patients living in countries with government-supported health-care systems limited in financial resources, graft rejection is a major concern. A study from Brazil using BM as the source of stem cells and CY+BU as the conditioning regimen reported a rejection rate of 43% in heavily transfused patients;[16] in a study from India, 31% of the transplants performed in SAA patients were ineffective because of graft rejection.[17] In contrast, in a study where 62.3% of patients were

Table 3. Univariate analysis of factors influencing OS in the study population

	5-Year OS, n *(%)*	*(95% CI)*	P-*value*	*HR*	*(95% CI)*	P-*value*
Age at allo-HSCT						
< 21 Years ($n = 122$)	93 (76%)	(67–83)	0.523	1		
> 21 Years ($n = 176$)	132 (75%)	(68–81)		1.15	0.37–1.8	0.524
Time from diagnosis to allo-HSCT						
< 157 Days ($n = 149$)	76 (76%)	(68–82)	0.715	1		
> 157 Days ($n = 149$)	84 (75%)			1.09	0.69–1.68	0.71
Conditioning regimen						
ATG-based regimen ($n = 219$)	175 (80%)	(73–84)	0.003	1		
Other regimen ($n = 79$)	51 (65%)	(53–74)		1.92	1.2–3.02	0.005
Class of ATG						
Horse ATG ($n = 61$)	44 (72%)	(60–81)	0.237	1		
Rabbit ATG ($n = 158$)	133 (84%)	(76–88)		0.69	0.3–1.2	0.23
Multi-transfused (PBSC)						
No ($n = 86$)	68 (79%)	(68–86)		1		
Yes ($n = 118$)	91 (77%)	(68–83)	0.278	1.36	0.77–2.3	0.28
Source of HSC						
Bone marrow ($n = 94$)	69 (74%)	(63–82)	0.954	1		
PBSC ($n = 204$)	157 (76%)	(70–82)		1.014	0.63–1.62	0.95
GvHD prophylaxis						
CsA+MTX ($n = 239$)	184 (77%)	(70–81)	0.28	1		
Other ($n = 59$)	42 (72%)	(59–82)		1.020	0.84–1.23	0.84
Year of transplant						
⩽2005 ($n = 125$)	86 (69%)	(60–76)	0.04	1		
After 2006 ($n = 173$)	140 (81%)	(74–86)		0.62	0.39–0.99	0.46
aGvHD II–IV						
No ($n = 205$)	186 (91%)	(86–94)		1		
Yes ($n = 93$)	40 (43%)	(29–56)	< 0.0001	6.9	(4.1–11.6)	< 0.0001
aGvHD III–IV						
No ($n = 272$)	242 (89%)	(84–92)		1		
Yes ($n = 26$)	1 (5.3%)	(0.5–22)	> 0.0001	14	6.9–28.1	< 0.0001
cGvHD						
No ($n = 143$)	120 (84%)	(78–88)		1		
Yes ($n = 155$)	102 (66%)	(53–76)	< 00001	2.40	1.4–3.9	0.001
cGvHD extensive						
No ($n = 245$)	206 (84%)	(78–88)		1		
Yes ($n = 53$)	23 (43%)	(23–62)	< 0.0001	4.3	2.4–7.7	< 0.0001

Abbreviations: aGvHD = acute GvHD; allo-HSCT = allogeneic haematopoietic stem cell transplant; ATG = anti-thymocyte globulin, CI = confidence interval; cGvHD = chronic GvHD; CsA = cyclosporine; HR = hazard ratio; MTX = methotrexate; OS = overall survival.

considered high risk based on, among other factors, multiple previous transfusions, 90% were transplanted using FLU-based regimens and PBSCs, achieving successful grafting in 96% and a 5-year OS of 75.5%.[18] The observation that high-risk patients may achieve durable engraftment with PBSCs has also been reported in a study conducted in the United States, where 26 patients achieved definite engraftment with CY and an ATG+FLU combination but at the cost of a high incidence of aGvHD and cGvHD.

Exploring secondary GF with PBSCs and BM, large studies have reported an incidence of 1.4–6% and 1.3–12%, respectively.[2,3] In our study, secondary graft rejection was 18% vs 13% ($P = 0.75$) with BM and PBSCs, respectively, and this was considered to be related to the conditioning regimen, not to the source of stem cells, as significantly more patients who lost their grafts did not receive ATG as part of their conditioning regimen.

Considering patients who developed AML or a myelodysplastic syndrome, it is important to underscore that they could have been misdiagnosed as having SAA or may have developed clonal evolution related to exposure to alkylating agents; it has also been reported that patients with Fanconi anaemia may present with a constellation of malignancies such as the patient who developed tongue cancer.

Our study has several limitations, including its retrospective design, the relatively small number of patients in the BM group and the lack of complete blood transfusion history in the BM patients; nonetheless, it provides the first general perspective of the treatment of SAA in Latin America.

In conclusion, our experience with BM and PBSCs as sources of stem cells has shown that successful engraftment is possible for patients in countries with limited resources. The use of CY and ATG or the ATG+FLU combination was a predictor of definite engraftment as an excessive secondary GF was seen with other conditioning regimens. Ideally, the use of BM as the source of stem cells should be the standard of care; however, PBSCs in this real-world scenario might be an option in selected cases such as

Table 4. Multivariate analysis of covariates influencing survival

Covariate	*HR*	*(95% CI)*	P-*value*
Multivariate analysis			
ATG in conditioning			
ATG-based regimen ($n = 219$)	1		
Other regimen ($n = 79$)	1.13	0.65–1.98	0.65
aGvHD II–IV			
No	1		
Yes	2.50	1.1–5.6	0.028
aGvHD III–IV			
No	1		
Yes	8.3	3.4–20.2	< 0.001
cGvHD			
No	1		
Yes	1.15	0.53–2.5	0.71
cGvHD extensive			
No	1		
Yes	1.09	0.45–2.6	0.83
Year of transplant			
$\leqslant 2005$ ($n = 125$)	1		
After 2006 ($n = 173$)	0.54	0.3–0.98	0.04

Abbreviations: aGvHD = acute GvHD; ATG = anti-thymocyte globulin, CI = confidence interval; cGvHD = chronic GvHD; HR = hazard ratio.

failure of a BM transplant or in heavily transfused patients as the increased risk of GvHD with PBSCs seems to outweigh the complications related to the prolonged aplastic phase or primary graft failure seen in BM transplants in high-risk patients living in countries with limited government-supported health-care systems.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHOR CONTRIBUTIONS

AV-M, DG-A, JRN-C, VA-P, VM, GJ, LV-G, AK-A, AB-A and GJR-A conceived the study, executed the statistical analysis and drafted the manuscript; JCJ-P and CHG-A designed the study and contributed to the manuscript; JG, ALB, SS, GB, SG, AR, SY, GK, JA, JMR, GJ, LR, CF, JV-O, EP-M, SG, EG-L, MAH-R, MMG-A, EH-M, MP-I, GR-G and MAGR-E contributed gathering the information and executing the statistical analysis.

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Supplementary Information accompanies this paper on Bone Marrow Transplantation website (http://www.nature.com/bmt)