Donor age influences graft-versus-host-disease-relapse-free survival after allogeneic stem cell transplant in elderly patients in two countries from Latin America

Berro Mariano  
*HSCT Unit, Hospital Universitario Austral, Pilar, Argentina*, mberro@cas.austral.edu.ar

Nelson Hamerschlak  
*HSCT Unit, Hospital Israelita Albert Einstein, San Pablo, Brazil*

Milovic Vera  
*HSCT Unit, Hospital Aleman, Buenos Aires, Argentina*

Castro Belen  
*HSCT Unit, Hospital Privado de Cordoba, Cordoba, Argentina*

García P. Andres  
*HSCT Unit, Hospital Privado de Cordoba, Cordoba, Argentina*

*See next page for additional authors*

Follow this and additional works at: [https://www.hosct.org/hematology-oncology-and-stem-cell-therapy](https://www.hosct.org/hematology-oncology-and-stem-cell-therapy)

**Recommended Citation**  
Mariano, Berro; Hamerschlak, Nelson; Vera, Milovic; Belen, Castro; Andres, García P.; Gonzalo, Ferini; Jos, Real J.; Adriana, Vitriu; Alberto, Gimenez C.; Georgina, Bendek; Sebastian, Yantorno; Juliana, Martinez R.; Martin, Saslavsky; Sol, Jarchum; Amalia, Cerutti; Cinthya, Correa da S.; Morgani, Rodrigues; Leandro, Riera; Jorge, Arbelbide; Gustavo, Kusminsky; and Lisa, Basquiera A. (2022) "Donor age influences graft-versus-host-disease-relapse-free survival after allogeneic stem cell transplant in elderly patients in two countries from Latin America," *Hematology/Oncology and Stem Cell Therapy*: Vol. 16 : Iss. 4 , Article 5.  
Available at: [https://doi.org/10.56875/2589-0646.1042](https://doi.org/10.56875/2589-0646.1042)

This Original Research Report is brought to you for free and open access by Hematology/Oncology and Stem Cell Therapy. It has been accepted for inclusion in Hematology/Oncology and Stem Cell Therapy by an authorized editor of Hematology/Oncology and Stem Cell Therapy.
Donor age influences graft-versus-host-disease-relapse-free survival after allogeneic stem cell transplant in elderly patients in two countries from Latin America

Authors

This original research report is available in Hematology/Oncology and Stem Cell Therapy: https://www.hosct.org/hematology-oncology-and-stem-cell-therapy/vol16/iss4/5
Donor Age Influences Graft-Versus-Host Disease Relapse-Free Survival after Allogeneic Stem Cell Transplant in Elderly Patients in Two Countries from Latin America

Berro Mariano a,*, Nelson Hamerschlak b, Milovic Vera c, Castro Belén d, García P. Andrés e, Ferini Gonzalo e, Real J. José c, Vitriu Adriana f, Gimenez C. Alberto e, Bendek Georgina e, Yantorno Sebastián g, Martinez R. Juliana h, Saslavsky Martin h, Jarchum Sol i, Cerutti Amalia k, Correa da S. Cinthya b, Rodrigues Morgani b, Riera Leandro i, Arbelbide Jorge e, Kusminsky Gustavo a, Basquiera A. Lisad on behalf of GATMO-TC: Grupo Argentino de Trasplante de Medula Osea y Terapia Celular

a HSCT Unit, Hospital Universitario Austral, Pilar, Argentina
b HSCT Unit, Hospital Israelita Albert Einstein, San Pablo, Brazil
c HSCT Unit, Hospital Aleman, Buenos Aires, Argentina
d HSCT Unit, Hospital Privado de Cordoba, Cordoba, Argentina
e HSCT Unit, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina
f HSCT Unit, Instituto Alexander Fleming, Buenos Aires, Argentina
g HSCT Unit, Hospital Italiano La Plata, La Plata, Argentina
h HSCT Unit, FUNDALEU, Buenos Aires, Argentina
i HSCT Unit, CETRAMOR, Rosario, Argentina
j HSCT Unit, Sanatorio Allende, Cordoba, Argentina
k HSCT Unit, Sanatorio Britanico, Rosario, Argentina
l HSCT Unit, CEMIC, Buenos Aires, Argentina

Abstract

Background and objectives: Allogeneic stem cell transplantation (Allo-SCT) in elderly patients is a growing practice. We aimed to determine the graft-versus-host disease (GVHD) relapse-free survival (GRFS) in patients ≥65 years who underwent Allo-SCT in two countries from Latin America.

Patients and methods: We performed a retrospective analysis of patients ≥65 years who underwent Allo-SCT in Argentina and Brazil from 2007 to 2019.

Results: Ninety-eight patients were evaluated, with primary diagnoses of acute myeloid leukemia and myelodysplastic syndrome; 30% of patients had a hematopoietic cell transplant-comorbidity index (HCT-CI) score ≥3 and 49% were in complete remission. Donor types included matched sibling (n = 41), matched unrelated (n = 31), and haploidentical (HID; n = 26) donors. The conditioning regimen was myeloablative in 28 patients (14 busulfan pharmacokinetically (PK)-guided) and reduced-intensity in 70 patients.

The two-year non-relapse mortality (NRM) was 29%, with a higher NRM in melphalan-based compared to other conditionings (51% vs. 33%, p = 0.02). The two-year relapse rate was 24%, with a reduction in PK-guided busulfan (0% vs. 28%, p = 0.03). The two-year overall survival (OS) and GRFS was 52% and 38%, respectively, with a significant reduction in GRFS in HCT-CI ≥3 (27% vs. others 42%, p = 0.02) and donors ≥40 years (29% vs. <40 years 55%, p = 0.02). These variables remained significantly associated with GRFS after multivariate analysis.
Conclusion: In this cohort of elderly patients from Argentina and Brazil undergoing Allo-SCT, donor age and comorbidities significantly influenced GRFS. The role of the conditioning regimen in this population deserves further investigation.

Keywords: Donor age, HSCT, GRFS

1. Introduction

Treatment of elderly patients with hematological malignancies is a therapeutic challenge. Several disease incidences, like acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS), increase with age [1]. The long-term prognosis is worse in older patients than in younger patients due to different aspects [2]. First, the biology of such pathologies is usually more aggressive in terms of molecular patterns [3]. Second, elderly patients frequently have higher comorbidity indexes and are more fragile and less likely to tolerate intensive treatments [4,5]. Despite this, allogeneic stem cell transplantation (Allo-SCT), as the only curative option for most patients, is increasingly performed [6,7].

Several studies have confirmed the potential benefit of transplant compared to conventional treatment in AML and MDS for older patients [8–10]. Ustun et al., in the South West Oncology Group (SWOG), Eastern Cooperative Oncology Group-American College of Radiology Imaging Network (ECOG-ACRIN), and Center for International Blood and Marrow Transplant Research (CIBMTR) collaborative study, compared transplant vs. no transplant in older AML patients with intermediate risk disease in first complete remission (CR); the Allo-SCT approach showed higher long-term overall survival (OS) [0.8]. Similarly, Platzbeck et al., on behalf of an international collaborative group, described a survival advantage for transplant vs. hypomethilating agents in patients with high-risk MDS or secondary AML [11].

It is uniformly believed that age is a risk factor for transplant outcome [12,13]. Sorror et al. demonstrated the independent significant impact of age in non-relapse mortality (NRM), adding one point to the hematopoietic cell transplant-comorbidity index (HCT-CI) score with recipient age of 40 years or more [12]. Nevertheless, the impact of age above 50–60 years is less clear. Atallah et al. described a similar survival outcome for MDS patients aged 65 years or older and those aged 55–64 years old who underwent transplantation [14]. On the other hand, Ringden, in a large European Society of Blood and Marrow Transplantation study, found a worse outcome for elderly patients ≥70 years compared to younger patients (60–69 years) [15].

Data about the outcome of Allo-SCT in elderly patients ≥70 years in our region is scarce [16,17]. In this population, survival free of the major complications of Allo-SCT becomes particularly important. We aimed to determine the graft-versus-host disease (GVHD) relapse-free survival (GRFS) in patients ≥65 years old who underwent Allo-SCT in Argentina and Brazil.

2. Patients and methods

We retrospectively reviewed a cohort of patients aged 65 years or older from 11 centers in Argentina and one center in Brazil who underwent Allo-SCT between 2007 and 2019. The following characteristics were evaluated: age, sex, disease, pre-transplant disease status, comorbidities (according to the HCT-CI score), donor type, stem cell source, conditioning, and immunosuppressive agents. Conditioning regimen, stem cell source, and antimicrobial prophylaxis were implemented according to institutional policies. The study was conducted following the Declaration of Helsinki. All patients signed informed written consent.

Acute GVHD (aGVHD) was graded according to the Glucksberg criteria; GRFS was calculated following Blood and Marrow Transplant Clinical Trials Network recommendations [18], and HCT-CI was based on an original publication. Neutrophil engraftment was defined as the first of two consecutive days above 500/mm³, and platelets engraftment as the first day above 20,000/mm³ without transfusion support in the previous 3 days. Disease status was defined as follows: CR in AML and MDS with less than 5% bone marrow blasts, lymphomas as standard definition; partial remission for MDS with 5–20% blasts or chemosensitive lymphomas not in CR; stable/progressive disease for the rest of the situations.

For the statistical analysis, easyR (1.33) was used. Acute and chronic GVHD (cGVHD), relapse, NRM, and engraftment incidence were analyzed with cumulative incidence (Grey test; NRM and relapse were the competing events for each other; relapse and NRM were the competing events for GVHD). OS, disease free survival, and GRFS were calculated using the Kaplan–Meier method (log-rank). Variables that had p ≤ 0.1 in univariate analysis were included in the multivariate analysis (MVA);
variables with missing values in more than 10% of patients were excluded. MVA for OS and GRFS was performed using Cox regression.

3. Results

Ninety-eight patients were enrolled, the median transplant year was 2016, the median patient age was 68 years (range 65–76), and 53 patients were male. The median follow-up time was 30 months. Prevalent diseases were AML (n = 47) and MDS (n = 34). Regarding comorbidities, 32 patients were high risk (HCT-CI ≥3); having diabetes and a previous solid tumor were the more frequent comorbidities. Donors were matched siblings (MSD; n = 41); unrelated (UD; n = 31), of whom 29 received anti-thymocyte globulin (ATG); and haploidentical donors (HID; n = 26), of whom all received post-transplant cyclophosphamide. The median donor ages were 66, 35, and 41 years for MSD, UD, and HID, respectively (p < 0.001). Conditioning regimen was myeloablative (MAC) in 28 patients (14 pharmacokinetically [PK]-guided with an area under the curve (AUC) between 4500 and 5000 μmol/min; 14 fixed dose), and reduced-intensity (RIC) in 70 patients, including busulfan-based in 31, melphalan-based in 26 (doses 100–140 mg/m2), and others in 13 patients. The main cohort characteristics, with donor type comparisons, are listed in Table 1.

Graft failure occurred in 5 patients (5%). At day 30, engraftment of neutrophils and platelets was 91% (95% confidence interval [CI] 83–95) and 67% (95% CI 57–76), respectively. For HID, neutrophil engraftment (17.5 days vs. 13.5 MSD and 15 UD, respectively; p = 0.03) and platelet engraftment (30.5 days vs. 15.5 MSD and 18.5 UD, respectively; p = 0.02) was achieved later compared to other donors. CMV reactivation was less likely to occur in MSD than HID and UD (25% vs. 34% vs. 41%, respectively; p = 0.01).

One year incidences of grades 2–4 (GII-IV) and 3–4 (GIII-IV) aGVHD were 38% (95% CI 28–48) and 13.5% (95% CI 7.6–21), respectively; 2-year moderate-severe cGVHD incidence was 16% (95% CI 10–24). Patients who underwent HID transplants developed a lower incidence of aGVHD I-II than those who underwent MSD and UD transplants (1-year 19% vs. 39% vs. 55%; p = 0.03), and a trend toward a lower incidence of aGVHD III-IV (1-year 0% vs. 19% vs. 17%; p = 0.06) was observed with no significant difference in cGVHD incidence. Patients in CR before transplant developed a significantly lower incidence of aGVHD than those with other statuses (1-year GII-IV 27% vs. 50%, p = 0.02; and GIII-IV 4% vs. 19%, p = 0.03), with no significant difference in cGVHD. The only factor associated with a reduction in moderate/severe cGVHD was donor age (2-year 6% < 40 years vs. 21% ≥ 40 years; p = 0.05).

The 100-day and 2-year NRMs for the entire cohort were 15% (95% CI 9.1–23) and 29% (95% CI 20–39), respectively. No significant impact was observed when we compared patient age (as a continuous variable or ≥70 years), type of donor, donor age (2-year 13% < 40 years vs. 31% ≥ 40 years; p = 0.10), HCT-CI (2-year 33% ≥ 3 vs. 20% 0–2; p = 0.15), or MAC vs. RIC conditioning. Melphalan RIC was associated with a significant increase in NRM as compared to other conditionings (100 days and 2-year 30% and 51% vs. 10% and 23%; p = 0.02) (Fig. 1). The two-year relapse rate was 24% (95% CI 16–24). No significant impact was observed with patient age, donor type, and donor age (2-year 13% < 40 years vs. 29% 40 ≥ years; p = 0.13), conditioning (MAC vs. RIC), and disease and pretransplant status. We compared PK-guided busulfan (14 patients with MAC) and other conditioning, with a significant reduction in relapse rate (2-year 0 vs. 28%; p = 0.03) (Fig. 2).

The two-year OS was 52% (95% CI 41–62). Melphalan RIC (2-year melphalan RIC 27% vs. others 59%; p = 0.01) and high HCT-CI (2-year HCT-CI ≥3 38% vs. HCT-CI 0–2 56%; p = 0.05) were associated with a lower OS. One- and two-year GRFS were 41% (95% CI 31–51) and 38% (95% CI 28–48), respectively. Factors associated with a lower GRFS were donor age (2-year <40 years 55% vs. ≥40 years 29%; p = 0.02) (Fig. 3), high HCT-CI (2-year HCT-CI 0–2 42% vs. HCT-CI ≥3 27%; p = 0.02), pretransplant status (2-year CR 51% vs. other status 19%; p = 0.006), and melphalan RIC (2-year melphalan RIC 13% vs. other regimes 44%; p = 0.03). For GRFS multivariate analysis, pretransplant status (due to high missing values as indicated in the methods) and melphalan RIC (due to dosing heterogeneity) were excluded. After adjusting with confounding factors, donor age ≥40 years (hazard ratio [HR] 2.69, 95% CI 1.13–6.38) and HCT-CI ≥3 (HR 2.11, 95% CI 1.14–3.91) were the only independently significant factors associated with GRFS (Table 2), even after adjusting for type of donor, transplant year, and source.

4. Discussion

In this retrospective cohort analysis, we observed that allogeneic transplant is feasible in an elderly population aged ≥70 years in our region. Around half of the patients will be alive at 2 years, and 40% will be free of relapse and the major transplant...
complications. Outcomes compared favorably with published data [19,20]; this reflects an improvement compared to previous publications of our group, even in a more elderly population [16]. The results are based on a low relapse incidence of around a quarter of the population, NRM below one third of the cohort, and approximately 15% of severe aGVHD and moderate to severe cGVHD, respectively.

Although pre-transplant assessment is important in every patient, in this specific population this becomes even more relevant. Disease status before transplant and comorbidities were the most relevant patient factors in the analysis. Patients in CR experienced less aGVHD and higher GRFS than those with other statuses; this supported findings from the ATG prospective trial by Finke et al. [21] Similarly, high-risk HCT-CI patients developed a non-significantly higher NRM rate, lower OS, and GRFS. As described by Sorror in 2014, the combination of comorbidities and age is crucial in tailoring

Table 1. Cohort characteristics (N=98).

<table>
<thead>
<tr>
<th></th>
<th>Cohort (N = 41)</th>
<th>MSD (N = 26)</th>
<th>Haplo (N = 31)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median, years)</td>
<td>68</td>
<td>69</td>
<td>68</td>
<td>0.77</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>62 (63)</td>
<td>17 (65)</td>
<td>21 (67)</td>
</tr>
<tr>
<td>Donor, sex</td>
<td>Male</td>
<td>53 (54)</td>
<td>21 (81)</td>
<td>16 (57)</td>
</tr>
<tr>
<td>Donor age</td>
<td>&lt;40 years</td>
<td>33 (33)</td>
<td>41</td>
<td>33</td>
</tr>
<tr>
<td>Disease</td>
<td>Acute Myeloid Leukemia</td>
<td>49 (50)</td>
<td>10 (40)</td>
<td>15 (48)</td>
</tr>
<tr>
<td></td>
<td>Myelodysplastic Syndrome</td>
<td>33 (33)</td>
<td>14 (56)</td>
<td>9 (29)</td>
</tr>
<tr>
<td></td>
<td>Others</td>
<td>16 (17)</td>
<td>2 (8)</td>
<td>7 (23)</td>
</tr>
<tr>
<td>Donor</td>
<td>Match Sibling Donor</td>
<td>41 (42)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Haploidentical Donor</td>
<td>26 (26)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unrelated Donor</td>
<td>31 (32)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-transplant status</td>
<td>Complete remission</td>
<td>48 (49)</td>
<td>16 (67)</td>
<td>12 (44)</td>
</tr>
<tr>
<td></td>
<td>Partial remission</td>
<td>9 (9)</td>
<td>5 (14)</td>
<td>3 (12)</td>
</tr>
<tr>
<td></td>
<td>SD/PD</td>
<td>29 (29)</td>
<td>5 (21)</td>
<td>14 (52)</td>
</tr>
<tr>
<td></td>
<td>Missing</td>
<td>12 (12)</td>
<td>0 (0)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>HCT-CI score</td>
<td>Low risk</td>
<td>32 (33)</td>
<td>9 (35)</td>
<td>9 (32)</td>
</tr>
<tr>
<td></td>
<td>Intermediate risk</td>
<td>28 (28)</td>
<td>8 (31)</td>
<td>8 (29)</td>
</tr>
<tr>
<td></td>
<td>High risk</td>
<td>29 (30)</td>
<td>9 (34)</td>
<td>11 (39)</td>
</tr>
<tr>
<td></td>
<td>Missing</td>
<td>12 (12)</td>
<td>3 (3)</td>
<td></td>
</tr>
<tr>
<td>Conditioning</td>
<td>Myeloablative</td>
<td>28 (28)</td>
<td>4 (15)</td>
<td>14 (45)</td>
</tr>
<tr>
<td></td>
<td>RIC, busulfan based</td>
<td>31 (32)</td>
<td>9 (34)</td>
<td>8 (26)</td>
</tr>
<tr>
<td></td>
<td>RIC, melphalan based</td>
<td>26 (26)</td>
<td>8 (31)</td>
<td>8 (26)</td>
</tr>
<tr>
<td></td>
<td>RIC, others</td>
<td>13 (12)</td>
<td>5 (19)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Source</td>
<td>Bone Marrow</td>
<td>30 (31)</td>
<td>12 (46)</td>
<td>6 (19)</td>
</tr>
<tr>
<td></td>
<td>Peripheral blood stem cell</td>
<td>68 (69)</td>
<td>14 (54)</td>
<td>25 (81)</td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>CNI + Mtx/MMF</td>
<td>34 (35)</td>
<td>0 (0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>ATG + CNI + Mtx/MMF</td>
<td>32 (33)</td>
<td>0 (0)</td>
<td>28 (93)</td>
</tr>
<tr>
<td></td>
<td>PTCy + CNI + Mtx/MMF</td>
<td>28 (28)</td>
<td>0 (0)</td>
<td>2 (7)</td>
</tr>
<tr>
<td></td>
<td>Missing</td>
<td>4 (4)</td>
<td>0 (0)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Transplant year (median 2016)</td>
<td>2007–2015</td>
<td>40 (41)</td>
<td>7 (27)</td>
<td>13 (42)</td>
</tr>
<tr>
<td></td>
<td>2016–2019</td>
<td>58 (59)</td>
<td>19 (73)</td>
<td>18 (58)</td>
</tr>
</tbody>
</table>

Definitions: MSD, matched sibling donor; Haplo, haploidentical donor; UD, unrelated donor; SD/PD, stable disease/progressive disease; HCT-CI, hematopoietic cell transplant/comorbidity index; RIC, reduced intensity; ATG, antithymocite globulin; CNI, calcineurin inhibitor; Mtx/MMF, methotrexate or mycophenolate; PTCy, XXX.

Fig. 1. Non-relapse mortality according to conditioning regimen. The melphalan-based reduced-intensity conditioning regimen significantly increased non-relapse mortality. Mel, melphalan; RIC, reduced-intensity conditioning.
conditioning [14]. A similar NRM after MAC compared to that after RIC supports their conclusions that even in elderly patients, myeloablation can be administered in selected patients. The selection of the best conditioning once the intensity is defined is less clear. Although this study was not designed to answer this question, PK-guided busulfan conditioning was superior in terms of relapse rate, with no significant differences in NRM, although they were all myeloablative conditionings. Several papers have addressed this hypothesis [22–24]. An American Society of Blood and Marrow Transplantation practice guideline committee stated that daily intravenous dose of busulfan is not inferior to a 6-h regimen and that there was not sufficient data to confirm the superiority of PK-guided busulfan [22]. Andersson et al. demonstrated in a prospective trial that PK-guided busulfan was superior to fixed dose in AML/MDS patients due to lower relapse and NRM [23]. On the contrary, melphalan-based RIC was associated with inferior outcomes associated with higher NRM. Patients received a wide range of melphalan doses, mainly from 100 to 140 mg/m²; thus, no conclusions can be obtained from our findings. Ciurea et al. demonstrated the safety of melphalan-based RIC regimes with a fixed dose of 100 mg/m² [25]. Melphalan 100 was superior to melphalan 140 mg/m², PK-guided busulfan 4000 (AUC total dose 16,000 \( \text{m}\text{mol/min} \)) and PK-guided busulfan \( \geq 5000 \) (AUC total dose \( \geq 20,000 \) \( \text{m}\text{mol/min} \)) in a large retrospective trial from the MD Anderson Cancer Center. Melphalan 100 patients showed almost 50% progression free survival (PFS) at 3 years compared to 23–34% for those with other conditionings and around 30% GRFS compared to less than 20%.

The most relevant finding of our analysis is the confirmation of the relevance of donor age in elderly transplant outcomes. In accordance with previous publications, older donors were associated with a non-significant increment in NRM and relapse rate, likely due to population size; a higher moderate-severe cGVHD and a significant reduction in the main objective of the analysis with a more than 2-fold increase in the risk of GRFS. Finke et al., in a UD prospective trial that evaluated the role of ATG, described a better outcome for donors less than 40 years due a lower aGVHD, cGVHD, and higher OS than older donors [21]. Similar findings were described in a CIBMTR study with more than 10,000 patients, by defining donor age as the most relevant factor associated with UD transplant survival [26].

Table 2. GRFS multivariate analysis.

<table>
<thead>
<tr>
<th></th>
<th>P</th>
<th>Hazard Ratio</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donor age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \geq 40 ) years</td>
<td>0.02</td>
<td>2.69</td>
<td>1.13</td>
<td>6.38</td>
</tr>
<tr>
<td>HCT-CI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High risk (( \geq 3 ))</td>
<td>0.01</td>
<td>2.11</td>
<td>1.14</td>
<td>3.91</td>
</tr>
<tr>
<td>Donor type</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSD</td>
<td>Ref.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haplo</td>
<td>0.33</td>
<td>0.67</td>
<td>0.30</td>
<td>1.50</td>
</tr>
<tr>
<td>UD</td>
<td>0.34</td>
<td>1.54</td>
<td>0.63</td>
<td>3.78</td>
</tr>
<tr>
<td>Transplant year</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2016–2019</td>
<td>0.05</td>
<td>0.55</td>
<td>0.30</td>
<td>1.01</td>
</tr>
<tr>
<td>Source</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral Blood</td>
<td>0.83</td>
<td>1.06</td>
<td>0.57</td>
<td>1.97</td>
</tr>
</tbody>
</table>

GRFS: graft-vs.-host disease, relapse-free survival; HCT-CI hematopoietic cell transplant-comorbidity index; Haplo, haploidentical donor; MSD, matched sibling donor; UD, unrelated donor.

**Fig. 2.** Relapse incidence according to conditioning regimen. Pharmacokinetically-guided busulfan resulted in a significant reduction in relapse incidence. PK, pharmacokinetically.

**Fig. 3.** Graft-versus-host disease relapse-free survival according to donor age. Donors younger than 40 years were associated with a significant improvement in graft-versus-host disease relapse-free survival.
higher incidence of GVHD in older donors with clonal hematopoiesis engraftment [27].

Moreover, donor age was an independently significant factor, even when compared with donor type. Kroger, in a myelodysplastic transplant review, concluded that younger unrelated donors might be a better selection than older MSD for MDS patients above 50 years. In a single-center retrospective analysis from Hamburg, younger UD were associated with higher long-term OS compared to older UD and MSD in patients transplanted for AML in CR [28]. The better outcome was due to a lower NRM (5 years 12% vs. 35%) and relapse rate (23% vs 33%) for UD < 40 years compared to MSD ≥40 years. The debate is still open since conflicting data have been published in this matter [19].

Other factors related to the patient or donor might affect transplant outcome. Particularly in elderly populations, geriatric assessment is an important tool that can predict survival [29–32]. Pamukcuoglu et al., in a single-center analysis, showed a 2-fold increase in early toxicities and 3-fold increase in mortality for patients defined as frail by Fried's score.30 Similarly, a group from San Francisco, California, observed an impairment in OS and PFS for the patients with deficits in any instrumental activities of daily living [31]. Finally, a CIBMTR analysis confirmed the independently significant impact of pre-transplant cognitive impairment in NRM for older patients after Allo-SCT [32].

The retrospective nature and the population size are two clear weaknesses of our study. Human leukocyte antigen compatibility data was not available for half of the UD patients, addressing a possible limitation in the GVHD analysis. Because information on conditioning heterogeneity and pre-transplant status was missing, these data were excluded from the multivariate analysis. Lastly, comprehensive geriatric assessment could not be included.

In conclusion, in our study of elderly patients from two countries from Latin America who underwent Allo-SCT, pre-transplant status, comorbidities, and donor age influenced the composite GRFS outcome. The role of the conditioning regimen in this population deserves further investigation.

Funding

There is no funding to disclose.

Author contribution

MB and BAL designed the study; MB and BAL prepared the manuscript and analyzed the data; MB, NH, MV, CB, GPA, FG, RJJ, VA, GCA, BG, YS, MRJ, SM, JS, CA, CSC, RM, RL, AJ, KG and BAL revised the manuscript.

Declaration of Competing Interest

There is no relevant conflict of interest to disclose.

References


