Outcome of Allogeneic Hematopoietic Stem Cell Transplant Recipients Admitted to the Intensive Care Unit with a Focus on Haploidentical Graft and Sequential Conditioning Regimen: Results of a Retrospective Study

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Outcome of allogeneic hematopoietic stem cell transplant recipients admitted to the intensive care unit with a focus on haploidentical graft and sequential conditioning regimen: results of a retrospective study (2010-2017)

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Abstract (349 words)

Background

Over the past decades, advances in allogeneic hematopoietic stem cell transplantation (alloHSCT) and critical care management have resulted in a significant improvement in outcome of critically ill alloHSCT recipients. Recently, haploidentical transplantation developed to overcome HLA-matched donor shortage and sequential conditioning regimens have been proposed for the treatment of refractory/relapsed hematological malignancies. Whether these new transplantation procedures affect the prognosis of critically ill alloHSCT recipients remains unknown.

Methods

A retrospective study including all consecutive alloHSCT patients admitted for the first time to the medical intensive care unit (ICU) of a tertiary academic center from 2010 to 2017.

Results

During the study period, 412 alloHSCTs were performed and 110 (27%) patients - median age 55 [range, 36-64] years, median time after allograft 58.5 [14-245] days - were admitted to ICU. Eighty-one (74%) had received a HLA-matched graft and 29 (26%) a haploidentical graft. Conditioning regimens were as follows: 40 (36%) reduced intensity conditioning (RIC), 36 (33%) myeloablative conditioning (MAC) and 34 (31%) sequential conditioning. At ICU admission, 28 (25%) patients presented

with acute graft-versus-host disease (aGVHD) ≥grade 2 and 44% with an uncontrolled hematological malignancy. Median SOFA score was 9 [6-11]. Invasive mechanical ventilation (MV) was required in 61 (55%) patients; vasopressors in 51 (46%) and renal replacement therapy in 16 (15%). Fifty-six (51%) patients died in the hospital. Sequential conditioning was independently associated with increased in-hospital mortality (OR=3.7 95%CI [1.14-12.92], P=0.033) and decreased overall survival (HR=1.86 [95% CI 1.05-3.31, P=0.03). Median survival after ICU admission was 20 days 95% CI [14;84] vs 231 days [95% CI 53;NA] and 206 days [95% CI 20;NA] in MAC and RIC patients, respectively (P=0.0004). Other independent factors associated with reduced overall survival were: hematopoietic cell transplantation-specific comorbidity index ≥2 (HR=1.76 [95% CI 1.10-2.84], P=0.02), aGVHD grade ≥ 2 (HR=1.88 [95% CI 1.14-3.10], P=0.01), MV (HR=2.37 [95% CI 1.38-4.07, P=0.002) and vasopressors (HR=2.21 [95% CI 1.38-3.54], P=0.001). Haploidentical transplantation did not affect outcome.

Conclusion

This study provides knowledge about the impact of new alloHSCT procedures on prognosis of critically ill alloHSCT patients that may help hematologists and intensivists in the management of these patients.

Keywords: allogeneic stem cell transplantation; haploidentical transplantation; transplantation conditioning; critical care; survival

Background

Allogeneic hematopoietic stem cell transplantation (alloHSCT) represents the only potentially curative treatment for a variety of malignant and nonmalignant hematological diseases [1] such as high-risk acute myeloblastic or lymphoblastic leukemia, myelodysplastic syndromes and myeloproliferative syndromes, high-risk lymphoma and aplastic anemia. However, a high rate of infections and severe specific complications [2] – conditioning regimen toxicity, graft rejection, graft-versus-host disease (GVHD) [3], thrombotic microangiopathy [4] and sinusoidal obstruction syndrome – can offset the benefit of alloHSCT. These potentially life-threatening adverse events, require intensive care unit (ICU) admission in 13% to 30% of alloHSCT recipients [5–24].

Over the past decades, advances have been made in the transplantation practice resulting in a significant improvement in the outcome of alloHSCT recipients. In France, one-year survival increased from 68.1% to 74.1% among patients transplanted between 2003-2009 and 2010-2017, respectively [25]. Reduction in non-relapse related mortality accounts for most of this improvement. Compared to myeloablative conditioning (MAC) regimens, reduced-intensity conditioning (RIC) has largely decreased the toxicity of conditioning [8,26]. The use of peripheral blood hematopoietic stem cells rather than bone marrow results in faster hematopoietic and immunologic reconstitution [27]. A better understanding of immunological processes has improved prevention and treatment of GVHD [28].

Concomitantly, significant progress in critical care management has been made.

Earlier admission, less-invasive management and modification in ICU triage policies have all contributed to improve the prognosis of alloHSCT recipients admitted to ICU. Lengliné *et al.* in a study comparing two cohorts of alloHSCT patients admitted to three French ICU from 1997 to 2003 and from 2004 to 2011, showed an increase in 90-day survival from 31% to 49% [7]. A recent meta-analysis combining data from 18 studies published between 2006 and 2016 including 2342 patients confirmed this improvement: the ICU mortality rate was 63.9% in patients admitted before 2004 and decreased to 37.2% after 2004 [23].

Moreover, the number of alloHSCT is continuously increasing. According to the annual survey of the European Society for Blood and Marrow Transplantation, 17,155 alloHSCT were performed in 2017 in Europe, representing a 40% increase compared to 2010 [29]. Haploidentical transplantation now enables patients lacking a HLA-matched donor, access to alloHSCT [25,30,31], but increases immunological conflict. Finally, patients with refractory/relapsed hematological malignancies can benefit from sequential conditioning regimens, which improve disease control, thereby increasing overall survival in this population [32,33]. These new alloHSCT procedures could potentially increase the risk of organ failure requiring ICU admission and worsen the prognosis of critically ill alloHSCT recipients.

The present study describes the outcome of alloHSCT recipients reflecting new transplantation practices, in particular haploidentical transplantation and use of sequential conditioning regimens, and aims to identify prognostic factors associated with in-hospital and overall survival.

Methods

Patients and settings

We conducted a retrospective study including all consecutive alloHSCT recipients admitted to the medical ICU of Saint-Antoine Hospital, Paris, France, from January 1, 2010 to December 31, 2017.

Admissions were identified through a systematic review of the hospital medico-administrative database using the International Classification of Diseases 10th revision (ICD-10) with codes Z94.8 “other transplanted organ and tissue status” and T86.0 “complications of bone marrow transplant”. Exclusion criteria were the following: autologous HSCT and admission for a scheduled procedure (central venous catheter insertion, bronchoscopy, renal replacement therapy). In the case of patients with more than one ICU admission, only the first admission was considered.

Allogeneic hematopoietic stem cell transplantation procedures

MAC included either fractionated total body irradiation (TBI) with more than 8 Gy, or a high-dose of an alkylating agent such as busulfan (>8 mg/Kg orally, 6.4 mg/Kg intravenously), or thiotepa (>10 mg/Kg) [34]. The sequential conditioning regimen for the majority of patients, consisted of a short course of intensive chemotherapy with total doses of thiotepa 10 mg/kg, etoposide 400 mg/m2, and cyclophosphamide 1600 mg/m2 on days -15 to -10, followed, by RIC with fludarabine 150 mg/m2, i.v. busulfan 6.4 mg/kg, and thymoglobulin 5 mg/kg on days -6 to -2. For patients aged >60 years and/or with comorbidities, total doses of thiotepa, etoposide, and cyclophosphamide were reduced [33]. Alternative

sequential conditioning regimens were FLAMSA-like [35,36] and clofarabine-based [32]. Other conditioning regimens were considered as RIC [37].

GVHD prophylaxis consisted of a combination of cyclosporine and mycophenolate mofetil, or cyclosporine and a short course of methotrexate. In the case of a haploidentical related donor, two doses of cyclophosphamide were infused after the cells were reinjected.

Acute GVHD (defined as $\geq$ grade II), was considered when patients were receiving systemic immunosuppressive treatment at the time of ICU admission. Methylprednisolone represented the first line treatment of acute GHVD [38].

Hematological characteristics

Neutropenia was defined as a neutrophil count under 500/µL.

Uncontrolled hematological malignancy at ICU admission was defined as either i) admission occurring in the 30 first days following alloHSCT for refractory/relapsed disease or ii) ongoing chemotherapy or targeted therapy for hematological disease relapse after alloHSCT or iii) ongoing treatment for post-transplant lymphoproliferative disorder.

ICU admission policy and management

Decision to admit to ICU arises from a concertation between hematologists and intensivists. During the ICU stay, diagnostic procedures, life-sustaining treatments and other therapies not related to alloHSCT were managed by the senior intensivist in charge of the patient. Specific therapies related to alloHSCT such as

immunosuppressive treatments, targeted therapies and chemotherapy or growth factors were prescribed after consultation with the senior hematologist. To withhold or withdraw life-sustaining treatment (when there was no hope of recovery) was decided in a decision-making process involving the hematologists in charge of the patient and the ICU physicians and nursing staff. Organ dysfunction was defined by a sequential organ failure assessment (SOFA) score ≥ 1 for the corresponding organ system.

Data collection

Data regarding underlying hematological disease, disease status at the time of alloHSCT and ICU admission, transplantation characteristics and ICU management were recorded through a careful review of medical charts.

Statistical analysis

Continuous variables were described as medians [interquartile ranges (IQRs)] and categorical variables as proportions. Comparisons of proportions between groups were made using Fisher's exact test. Comparisons of continuous variables between groups were made using the Wilcoxon rank-sum test. The analysis of hospital mortality was based on logistic models. Univariate models were fitted, and then those associated with the outcome at the 0.2 level were introduced into a multivariate model, with variable selection based on the Akaike criterion. The log-linearity assumption was checked, and variables were tested for collinearity before inclusion in the multivariate model. Goodness of fit was evaluated using Le Cessie-

van Houwelingen's method and model discrimination with the AUC statistic. Predictive factors of overall survival were assessed using cause-specific Cox models, with model selection similar to that described above. Cumulative incidence curves were plotted and compared across baseline groups using Gray's test. All tests were two-sided and p-values lower than 0.05 were considered to indicate significant associations. Analyses were performed using R statistical platform, version 3.0.2 (https://cran.r-project.org/).

Ethical considerations

All patients signed an anonymous data-recording consent before alloHSCT procedure.

The hospital database is declared to the national committee for protection of privacy (Commission Nationale de l'Informatique et des Libertés). The study has been approved by the Ethics commission of the French Intensive Care Society (Société de Réanimation de Langue Française).

Results

Patient and hematological characteristics

Patient and hematological characteristics are summarized by hospital survivors and non-survivors in Table 1.

We identified 275 ICU stays for which ICD-10 codes Z94.8 and T86.0 were recorded from January 1, 2010 to December 31, 2017. After exclusion of non-alloHSCT patients and multiple admissions, 110 patients were included in the study

(Supplemental Figure 1). Over the study period, 412 alloHSCT procedures were performed, representing an ICU admission rate of 27%.

Seventy-one (65%) patients were male. Median age was 55 years interquartile range (IQR [36-64]) and median hematopoietic cell transplantation-specific comorbidity index (HCT-CI) was 0 (IQR [1-2]). Acute leukemia - myeloblastic (44%) and lymphoblastic (19%) - constituted the main indication for alloHSCT, followed by myelodysplastic and myeloproliferative syndromes (17%) and other hematological malignancies (20%). Fifty-nine (54%) patients achieved complete remission before transplantation.

Peripheral blood stem cells represented the main graft source (89%). Eighty-one (74%) patients received a graft from a HLA-matched donor, and 29 (26%) from a familial haploidentical donor. During the study period, 107 haploidentical alloHSCTs were performed, leading to the same admission rate (27%) in both haploidentical and HLA-matched recipients (P=0.90). Three conditioning regimens were distributed as follows: 40 (36%) patients received RIC, 36 (33%) MAC, and 34 (31%) sequential conditioning, corresponding to an ICU admission rate of 33%, 20% and 30%, respectively (P=0.039).

ICU characteristics

ICU characteristics are summarized in Table 2.

Patients were admitted to ICU in a median time of 59 [IQR 14-245] days after allograft. Forty-seven (43%) patients were admitted to ICU within the first month following transplantation. At ICU admission, 28 (25%) patients were receiving

systemic immunosuppressive therapy for acute GVHD ≥grade 2, 48 (44%) presented with an uncontrolled hematological malignancy and 53 (48%) with neutropenia. Median simplified acute physiology score (SAPS) II was 50 [IQR 37-64] and median SOFA score was 9 [IQR 6-11]. Respiratory failure (77%) represented the most frequent organ dysfunction followed by acute kidney injury (58%), neurological (46%) and circulatory (45%) failure. Invasive mechanical ventilation was required by 61 (55%) patients; vasopressors by 51 (46%) patients and renal replacement therapy by 16 (15%). For 16 (15%) patients, a decision to forego life-sustaining treatments was taken. Forty (36%) patients died in the ICU (Supplemental Figure 1).

In-hospital mortality

More than half of the patients (n=56, 51%) died in the hospital (Supplemental Figure 1). In the univariate analysis, ICU characteristics associated with in-hospital mortality were: SAPS II (p=0.004), SOFA score at ICU admission (p=0.016), invasive mechanical (p<0.0001) and vasopressors (p=0.0006) (Table 2). Sequential conditioning was the only hematological factor associated with in-hospital mortality: 45% of patients who received this regimen died, versus 25% and 30% patients who received MAC and RIC, respectively (P=0.006) (Table 1). Compared to MAC and RIC patients, those who received sequential conditioning had more comorbidities, more frequently uncontrolled malignancy at ICU admission, were admitted to ICU earlier after graft procedure, for more severe critical illness, and presented more frequently with neutropenia (Supplemental Table 1). However, in the multivariate analysis, a

sequential conditioning regimen remained associated with in-hospital mortality (OR=3.7 [95% CI 1.14-12.92], p=0.033), as did invasive mechanical ventilation (OR= 8.44 [95% CI 3.30-23.19], p<0.001) (Table 3).

Moreover, among the 99 patients who were still in ICU at day 3, the evolution of organ dysfunctions, assessed by delta SOFA D3-D1 (difference between SOFA score at day 3 and day 1), was associated with hospital outcome. The in-hospital mortality rate was 28% in patients with improving organ dysfunction compared to 70% and 77% in patients with stable or worsening organ failure, respectively (P<0.0001). We observed a sigmoidal relationship between delta SOFA D3-D1 and probability of in-hospital mortality (Figure 1). Furthermore, delta SOFA D3-D1 had a better discrimination ability for in-hospital mortality (AUC=0.81 [95% CI 0.73-0.90]), than the SOFA score at day 1 (AUC=0.58 [95% CI 0.47-0.70]) or at day 3 (AUC=0.74 [0.65-0.85]).

Overall survival

Median survival was 2.49 [95% CI 1.02-7.02] months with a median follow-up of 2.49 [95% CI 0.44 -17.5] months. Eighty patients (73%) died during follow-up (Figure 3A). No difference in overall survival was observed between HLA-matched and haploidentical alloHSCT (P=0.83, Figure 3B). To the contrary, a sequential conditioning regimen was independently associated with decreased overall survival (HR=1.86 [95%CI 1.05-3.31], P=0.03) (Figure 2). Median survival after ICU admission was 20 [95%CI 14;84] days in patients who received sequential conditioning vs 231 [95% CI 53;NA] and 206 [95% CI 20;NA] days in MAC and RIC patients, respectively

(P=0.0004) (Figure 3C, Supplemental Table 1). In the multivariate analysis, other factors associated with a lower overall survival were: HCT-CI score ≥2 (HR=1.76 [95%CI 1.10-2.84], P=0.02), acute GVHD grade≥2 (HR=1.88 [95%CI 1.14-3.10], P= 0.01), mechanical ventilation (HR=2.37 [95%CI 1.38-4.07, P=0.002) and vasopressors (HR=2.21 [95%CI 1.38-3.54], P=0.001) (Figures 2, and Supplemental Figure 2).

Discussion

In this study, we report outcome and prognostic factors in 110 consecutive alloHSCT patients admitted to ICU in a recent time period (2010-2017). Interestingly, our cohort included patients who received sequential conditioning regimens for uncontrolled hematological malignancy (31%) and haploidentical graft recipients (26%). The potential influence of these new procedures on outcome of alloHSCT after ICU admission was not known. We found no impact of haploidentical transplantation on ICU admission rate and prognosis compared to phenoidentical and genoidentical grafts. A sequential conditioning regimen was independently associated with poorer short- and long-term prognosis. To the contrary, our study suggests improved overall survival among critically ill MAC and RIC patients compared to that reported in previous cohorts [6–8,13,22,23,39–43]. According to published data [6–8,23,39,41–45], mechanical ventilation, and persistent or worsening of organ failure at day 3 was associated with higher in-hospital mortality. We also confirmed that HCT-CI score ≥2 [5,44], active acute GVHD ≥grade 2 at ICU admission [7,46], invasive mechanical ventilation [43], and vasopressors [43] were independently associated with decreased overall survival.

Over the past few years, haploidentical grafts have been increasingly used as an alternative to matched donors [25,31]. However, the impact of this new procedure on outcome of alloHSCT recipients admitted to ICU has not been addressed before. Our cohort included about one quarter of haploidentical alloHSCT recipients. Large registry-based retrospective studies have demonstrated that haploidentical alloHSCT with posttransplant cyclophosphamide was associated with comparable outcomes to those of HLA-matched grafts [30,47–49]. Consistently, we have observed similar ICU admission rates, hospital and overall survival among patients who received haploidentical and HLA-matched grafts even after adjustment for potential confounders. This encouraging result needs to be confirmed by larger studies.

The second specificity of our cohort is to include about one third of patients treated with a sequential conditioning regimen for refractory/relapsed disease. AlloHSCT represents the only therapeutic option which can offer complete remission in this scenario. However, the toxicity of a MAC regimen is associated with high non-relapse mortality, and RIC regimens do not provide sufficient disease control [50]. Sequential conditioning, consisting of a short intensive chemotherapy followed by RIC, has been proposed as a new therapeutic option and is associated with a better survival than chemotherapy alone, ranging from 33% to 56% at 2 years [33,51,52]. Only one previous cohort of critically ill alloHSCT recipients has included patients who received sequential conditioning [44,53] and its impact on outcome was not known. In our study, sequential conditioning patients experienced a very poor prognosis with a median survival of 20 days and 1-year mortality reaching 74%,

whereas more than half of MAC and RIC patients were alive one year after ICU admission. This increase in mortality could be explained by more comorbidities, higher prevalence of uncontrolled malignancy at ICU admission and more severe critical illness. Nevertheless, sequential conditioning remained independently associated with increased in-hospital mortality and decreased overall survival, even after adjustment for these potential confounding factors. The toxicity of sequential conditioning could also account for this poorer outcome. This hypothesis is supported by the shorter delay between alloHSCT and ICU admission, and the higher early death rate associated with sequential conditioning compared to other regimens. Increased frailty secondary to refractory/relapsed disease and/or previous chemotherapy could represent an alternative explanation [54]. Unfortunately, we were unable to test this hypothesis.

Apart from sequential conditioning, mechanical ventilation was the only independent factor associated with in-hospital mortality. No other hematological characteristics were associated with short-term prognosis, in particular, hematological status at ICU admission. These results are consistent with previous studies [6–8,23,39,41–45] confirming the major role of organ dysfunction over hematological status in determining short-term outcome. Orvain *et al*. underlined that the number of organ dysfunctions prior to ICU admission, as well as the time between first organ failure and ICU admission, was associated with in-hospital mortality [53]. Platon *et al*. showed that the evolution of SOFA score between admission to ICU and day 3 was independently associated with ICU mortality [45]. In the same way, we observed a sigmoidal relationship between delta SOFA D3-D1 and

in-hospital mortality which dramatically increased in patients with persistent or worsening organ dysfunction. Moreover, delta SOFA D3-D1 had a better discrimination ability for in-hospital mortality than the isolated value of SOFA score at day 1 or at day 3. Finally, in the study by Lindgaard *et al*. [41], an ICU length of stay equal to or over 10 days was independently associated with increased mortality 6 months after ICU admission. Altogether these results suggest that i/ early admission is associated with better survival, ii/ an ICU trial might be an option for patients for whom prognosis remains uncertain and iii/ regular reappraisal of organ dysfunction is of major relevance in the decision-making process for the caring of the critically ill alloHSCT patient.

We reassessed overall survival and found that 37% of alloHSCT recipients were alive one year after admission to our ICU, which is consistent with recently reported 1-year mortality rates ranging from 61% to 87% [5,6,8,39,41–45]. However, our cohort included about one third of sequential conditioning patients who experienced a significantly poorer prognosis than MAC and RIC patients. Recent cohorts including MAC and RIC patients admitted to ICU from 2010 to 2013 [5,8,41–43,45] reported 1-year survival rates of between 13% and 39%. In our study, more than half of MAC and RIC patients (55%) were still alive one year after admission to ICU despite similar characteristics in terms of HCT-CI score, acute GVHD, severity of critical illness, need for invasive mechanical ventilation and vasopressors. These results corroborate ongoing improvement in long-term prognosis of critically ill MAC and RIC alloHSCT patients described previously [7,39,42,43]. We also confirmed that invasive mechanical ventilation [43], vasopressors [43], acute GVHD [42–44,46] and HCT-CI $\geq$

2 [5,44] were independently associated with decreased overall survival.

We acknowledge that this study has several limitations. The main ones being its small size and its single-center and retrospective design. Other limitations include the lack of information regarding performance status and/or frailty, which represent major prognosis factors in addition to HCT-CI [54]. Due to the limited number of haploidentical graft recipients included in our cohort, we cannot ignore the fact that our study was underpowered to detect an effect of haploidentical transplantation on outcome. To the contrary, despite the limited number of sequential conditioning patients, we observed that this regimen was significantly and independently associated with in-hospital mortality and overall survival. Our results need to be confirmed by larger, multicenter studies.

Conclusion

Severe complications requiring ICU admission occurred in one quarter of patients receiving an alloHSCT at our center. About half of the patients died in the hospital after ICU admission. In-hospital mortality was driven by severity of critical illness, need for mechanical ventilation and evolution of organ dysfunctions during the stay in ICU. Sequential conditioning for refractory/relapsed disease represented the only hematological factor associated with in-hospital mortality and was also a novel poor prognosis factor for overall survival. More than 90% patients who received this conditioning regimen died within one year after ICU admission. However, whether this unfavorable prognosis is related to the frailty of patients receiving sequential conditioning and/or to the toxicity of these conditioning regimens remains to be

determined. Our results also suggest ongoing improvement in long-term prognosis of critically ill MAC and RIC alloHSCT patients, with one-year survival reaching 55%. We confirm that invasive mechanical ventilation, vasopressors, acute GVHD and HCT-CI $\geq$2 were also independently associated with decreased overall survival. Interestingly, we did not find any impact of haploidentical graft on outcome. In summary, this study confirms previously known prognostic factors and provides knowledge on the impact of new alloHSCT procedures on outcome of critically ill alloHSCT patients that may help hematologists and intensivists in the management of these patients.

List of abbreviations

AlloHSCT: allogeneic hematopoietic stem cell transplantation

GHVD: graft-versus-host disease

HCT-CI: hematopoietic cell transplantation-specific comorbidity index

ICU: intensive care unit

IQR: interquartile range

MAC: myeloablative conditioning

RIC: reduced intensity conditioning

TBI: total body irradiation

SOFA: sequential organ failure assessment

SAPS II: simplified acute physiology score II

95% CI: 95% confidence interval

AUC: area under curve

Declarations

Ethics approval and consent to participate: all patients signed an anonymous data-recording consent before alloHSCT procedure. The hospital medico-administrative is declared to the national committee for protection of privacy (Commission Nationale de l'Informatique et des Libertés). The study has been approved by the Ethics commission of the French Intensive Care Society (Société de Réanimation de Langue Française).

Consent for publication: Not applicable.

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests: RD and MM received honoraria for lectures from Keocyt and Sanofi, whose drugs were used to treat patients included in this study.

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Author's contributions: conception and design: VG, GD, RD and NB; acquisition, analysis, or interpretation of data: VG, GD, RD and NB; drafting of manuscript and/or revising it for important intellectual content: VG, GD, RD and NB; final approval of version to be published: VG, GD, JRL, GH, TU, JLB, HAO, EM, BG, RD and

NB; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: VG and NB. All authors have read and approved the final manuscript.

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Table 1. Patients and hematological characteristics

	All patients	Hospital survivors	Hospital non survivors	P-value
Number of patients	110	54	56	
Characteristics of patients				
Males, n (%)	71 (65%)	36 (67%)	35 (62%)	0.69
Age in years, median [IQR]	55 [36-64]	51 [38-62]	57 [36-65]	0.32
HCT-CI, median [IQR]	0 [1-2]	1 [0-3]	1 [0-2]	0.33
HCT-CI $\geq$ 2	45 (41%)	18 (33%)	27 (48%)	0.13
Hematological disease				0.84
AML, n (%)	48 (44%)	22 (41%)	26 (46%)	
ALL, n (%)	21 (19%)	10 (19%)	11 (20%)	
MDS/MPS, n (%)	19 (17%)	11 (20%)	8 (14%)	
Other, n (%)	22 (20%)	11 (20%)	11 (20%)	
Complete remission before HSCT, n (%)	59 (54%)	32 (59%)	27 (48%)	0.26
Conditioning regimen				0.006
Reduced intensity, n (%)	40 (36%)	23 (43%)	17 (30%)	
Myeloablative, n (%)	36 (33%)	22 (41%)	14 (25%)	
Sequential, n (%)	34 (31%)	9 (17%)	25 (45%)	
Donor type				0.67
HLA-matched donor	81 (74%)	41 (76%)	40 (71%)	
HLA-haploidentical donor, n (%)	29 (26%)	13 (24%)	16 (29%)	
Stem cell source				0.60
Peripheral blood stem cells, n (%)	98 (89%)	47 (87%)	51 (91%)	
Bone marrow, n (%)	6 (5,5%)	4 (7%)	2 (4%)	
Cord blood cells, n (%)	5 (4,5%)	3 (6%)	2 (4%)	

Quantitative variables are expressed as median [25-75th percentiles] and qualitative variables as number (%).

Table 2. ICU characteristics

	All patients	Hospital survivors	Hospital non survivors	P-value
Number of patients	110	54	56	
Hematological characteristics at ICU admission				
Time from HSCT to ICU (days), median [IQR]	59 [14-245]	70 [22-364]	65 [26-204]	0.53
Time from HSCT to ICU < 30 days, n (%)	47 (43%)	24 (44%)	23 (41%)	0.85
Uncontrolled hematological malignancy, n (%)	48 (44%)	21 (39%)	27 (48%)	0.34
Acute GVHD ≥ grade 2, n (%)	28 (25%)	12 (22%)	16 (29%)	0.51
Aplasia at ICU admission, n (%)	53 (48%)	22 (41%)	31 (55%)	0.13
Severity scores at ICU admission, median [IQR]				
SAPS II	50 [37-64]	47 [33-56]	57 [41;81]	0.004
SOFA score	9 [6-11]	8 [6-10]	10 [6-12]	0.016
Organ dysfunctions at ICU admission, n (%)				
Respiratory failure	85 (77%)	42 (78%)	43 (77%)	1.0
Kidney failure	64 (58%)	31 (57%)	33 (59%)	1.0
Circulatory failure	50 (45%)	23 (43%)	27 (48%)	0.57
Neurological failure	51 (46%)	20 (37%)	31 (55%)	0.059
Hematological failure	101 (92%)	52 (96%)	49 (88%)	0.16
Life-sustaining therapies				
Invasive mechanical ventilation	61 (55%)	15 (26%)	48 (82%)	<0.0001
Vasopressors	51 (46%)	16 (30%)	35 (62%)	0.0006
Renal replacement therapy	16 (15%)	4 (7%)	12 (21%)	0.057
Decision to forego life sustaining treatments, n (%)	16 (15%)	0 (0%)	16 (29%)	<0.0001

Quantitative variables are expressed as median [25-75th percentiles] and qualitative variables as number (%).

	Odds ratio	95% CI	P-value
Conditioning regimen			
Myeloablative	-	-	-
Reduced intensity	1.23	[0.40-3.83]	0.714
Sequential	3.70	1.14-12.92	0.033
Vasopressors	2.47	0.94-6.59	0.066
Mechanical ventilation	8.44	3.30-23.19	<0.001

Table 3. Predictors of in-hospital mortality (multivariate analysis)

Legend to Figures

Figure 1. Probability of in-hospital mortality according to Delta SOFA D3 – D1

Figure 2. Factors associated with overall survival (multivariate analysis)

Figure 3. Cumulative incidence of death among the entire cohort (A) and according to the donor type (B) and to the conditioning regimen (C)

Additional files

Supplemental Table 1. Patients, hematological and ICU characteristics, and outcome according to conditioning regimen

	Myeloablative	Reduced intensity	Sequential	P-value
Number of patients	36	40	34	
Patients 'characteristics				
Age (years)	49 [34-59]	59 [56-65]	56 [41-65]	0.04
HCT-CI	0 [0-2]	1 [0-2]	2 [0-2]	0.16
HCT-CI ≥2	10 (28%)	16 (40%)	19 (56%)	0.017
Hematological characteristics at ICU admission				
Time from alloHSCT to ICU admission (days)	66 [18-347]	117 [24-448]	18 [9-63]	0.001
Neutropenia at ICU admission	16 (44%)	13 (33%)	24 (71%)	0.032
Uncontrolled hematological malignancy	13 (36%)	26 (40%)	25 (74%)	<0.0001
Acute GVHD ≥grade 2	11 (31%)	9 (23%)	8 (24%)	0.69
ICU characteristics				
SOFA score at ICU admission	8 [5-10]	9 [6-11]	10 [7-13]	0.032
Invasive mechanical ventilation	18 (50%)	18 (45%)	25 (74%)	0.0511
Vasopressors	13 (36%)	21 (53%)	17 (50%)	0.24
Renal replacement therapy	7 (19%)	5 (13%)	4 12%)	0.36
Outcome				
ICU mortality	10 (28%)	12 (30%)	18 (53%)	0.053
In-hospital mortality	14 (39%)	17 (43%)	25 (74%)	0.0062
Median survival (days)	231 [53-NA]	206 [20-NA]	20 [14-84]	0.0012
1-year mortality	16 (47%)	18 (45%)	3 (91%)	0.001

Quantitative variables are expressed as median [25-75th percentiles] and qualitative variables as number (%).Quantitative variables are expressed as median [95% CI].

Supplemental Figure 1. Flow chart of the study

Supplemental Figure 2. Cumulative incidence of death according to need for invasive mechanical ventilation (A), need for vasopressors (B), acute GHVD at ICU admission (C), and HCT-CI score (D).