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ORIGINAL ARTICLE

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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Abstract

Haploidentical transplantation has extended the availability of allogeneic hematopoietic stem cell transplant (alloHCT) to almost all patients. Sequential conditioning regimens have been proposed for the treatment of hematological active disease. Whether these new transplantation procedures affect the prognosis of critically ill alloHCT recipients remains unknown. We evaluated this question in a retrospective study including consecutive alloHCT patients admitted to the intensive care unit of a tertiary academic center from 2010 to 2017. During the study period, 412 alloHCTs were performed and 110 (27%) patients—median age 55 (36–64) years—were admitted to ICU in a median time of 58.5 (14–245) days after alloHCT. Twenty-nine (26%) patients had received a haploidentical graft and 34 (31%) a sequential conditioning. Median SOFA score was 9 (6–11). Invasive mechanical ventilation (MV) was required in 61 (55%) patients. Fifty-six (51%) patients died in the hospital. Independent factors associated with in-hospital mortality were as follows: MV (OR=8.44 [95% CI 3.30–23.19], $p<0.001$), delta SOFA between day 3 and day 1 (OR=1.60 [95% CI 1.31–2.05], $p<0.0001$), and sequential conditioning (OR=3.7 [95% CI 1.14–12.92], $p=0.033$). Sequential conditioning was also independently associated with decreased overall survival (HR=1.86 [95% CI 1.05–3.31], $p=0.03$). Other independent factors associated with reduced overall survival were HCT-specific comorbidity index ≥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], $p=0.01$), 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. Larger multicenter studies are warranted to confirm these results.

Keywords Allogeneic stem cell transplantation · Haploidentical transplantation · Transplantation conditioning · Critical care

Background

Allogeneic hematopoietic cell transplantation (alloHCT) represents the only potentially curative treatment for a variety of malignant and nonmalignant hematological diseases [1] mainly high-risk acute myeloblastic or lymphoblastic leukemia. Also, the number of alloHCT is increasing steadily. According to a recent survey from the European Society for Blood and Marrow Transplantation, the number of procedures has increased by 40% between 2010 and 2017, to reach more than 17,000 alloHCTs per year in European countries [2].

Over the past decades, major advances have been made in both transplantation practices and supportive care, resulting in a significant improvement in the outcome of alloHCT recipients [3], especially non-relapse-related mortality. This

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includes a better understanding of immunological processes which has improved prevention and treatment of GVHD [4] and the use of peripheral blood hematopoietic stem cells resulting in faster hematopoietic and immunologic reconstitution [5]. More recently, new conditioning regimens have been proposed and seem of great interest. For example, reduced-intensity conditioning (RIC) allows for a reduction in conditioning toxicity [6, 7], haploidentical transplantation now enables patients lacking a HLA-matched donor access to alloHCT [3, 8, 9], and patients with active disease can benefit from sequential conditioning regimens, which improve disease control, thereby increasing overall survival in this population [10, 11].

However, these patients remain at high risk for life-threatening complications requiring intensive care unit admission in up to 30% of alloHCT recipients [7, 12–30], with high reported mortality rate [14, 29]. In particular, it remains unclear how new transplantation procedures could have affected critically ill alloHCT recipient outcome.

Accordingly, we conducted a retrospective study to investigate features and outcomes of critically ill alloHCT recipients with a specific attention to conditioning regimens and haploidentical transplantation.

Methods

Patients and settings

We conducted a retrospective study including all consecutive alloHCT 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 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 or 6.4 mg/kg intravenously), and/or thiotepa (>10 mg/kg) [31]. The sequential conditioning regimen for the majority of patients consisted of a short course of intensive chemotherapy with total doses of 10 mg/kg thiotepa, 400 mg/m^2 etoposide, and 1600 mg/m^2 cyclophosphamide on days −15 to −10, followed, by RIC with 150 mg/m^2 fludarabine, i.v. 6.4 mg/kg busulfan, and 5 mg/kg thymoglobulin on days −6 to −2. For patients aged >60 years or with comorbidities, total doses of thiotepa, etoposide, and cyclophosphamide were reduced [11]. Alternative sequential conditioning regimens were FLAMSA-like [32, 33] and clofarabine-based [10]. Patients received a sequential conditioning if they had a refractory disease, as previously published [11]. Other conditioning regimens were considered RIC [34].

Haploidentical alloHCT was defined as transplantation with 5/10 HLA-identical donor.

GVHD prophylaxis consisted of a combination of cyclosporine, anti-thymocyte globulin (5 mg/kg), and mycophenolate mofetil, or cyclosporine and a short course of methotrexate. All haploidentical transplantation recipients received cyclophosphamide after the cells were reinjected. Most of them received two doses of 50 mg/kg/day. When bone marrow was used as source of stem cells or in case of cardiac toxicity, a single dose was administered.

Acute GVHD, defined as ≥grade II, was considered when patients were receiving systemic immunosuppressive treatment at the time of ICU admission. Methylprednisolone represented the first-line treatment [35]. Neutropenia was defined as a neutrophil count under 500/μL.

ICU admission policy and management

Decision to admit to ICU arises from a concertation between hematologists and intensivists. During the ICU stay, diagnostic procedures and therapies not related to alloHCT were managed by the senior intensivist in charge of the patient. Specific therapies related to alloHCT were prescribed after consultation with the senior hematologist. When there was no hope of recovery, the hematologists in charge of the patient, the ICU physicians, and the nursing staff participated to the decision to withhold or withdraw life-sustaining treatment.

Data collection

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

Statistical analysis

Quantitative variables are described as median and interquartile range (IQR) and compared using Wilcoxon's rank sum test; qualitative variables are shown as counts (percent) and compared using Fisher's exact test.

First, factors associated with hospital mortality were assessed using multivariate analysis by logistic regression. Variables achieving $p<0.20$ in univariate analyses were entered into the multivariate logistic regression model. A multiple backward-stepwise selection procedure eliminated those variables with an exit threshold set at $p = 0.05$, after testing for collinearity between variables and checking the assumption of log-linearity. Goodness of fit was evaluated using Le Cessie van Houwelingen's method and discrimination with AUC statistic.

Then, factors associated with overall survival were assessed using Cox regression 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 alloHCT 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

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-alloHCT patients and multiple admissions, 110 patients were included in the study (Supplemental Figure 1). Over the study period, 412 alloHCT procedures were performed, representing an ICU admission rate of 27%.

Patient and hematological characteristics are summarized in Table 1. Seventy-one (65%) patients were male. Median age was 55 (IQR [36–64]) years and median hematopoietic cell transplantation–specific comorbidity index (HCT-CI) was 1 (IQR [0–2]). Acute leukemia—myeloblastic (44%) and lymphoblastic (19%)—constituted the main indication for alloHCT, followed by myelodysplastic and myeloproliferative syndromes (17%) and other hematological malignancies (20%). Fifty-nine (54%) patients were in complete remission at transplant. The median number of treatment lines before transplant was 1 [1, 2] (0: n=7; 1: n=49; 2: n=39; 3: n=9; >3: n=6). Twenty-nine (26%) patients received a graft from a familial haploidentical donor. The other patients received graft from the following donors: 42 (38%) unrelated 10/10 HLA-matched donor, 27 (25%) genoidentical donor, 7 (6%) unrelated 9/10 HLA-matched donor, and 5 (4%) umbilical cord blood transplant. During the study period, 107 haploidentical alloHCTs were performed, leading a similar admission rate (27%) in both haploidentical and non-haploidentical 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) (Table 1). Among the 34 patients who received sequential conditioning regimen, three types of regimen were used: TEC-RIC (n=27, 79%), clofarabine-based (n=4, 12%), FLAMSA-like (n=3, 9%).

ICU characteristics

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 presented with acute GVHD ≥grade 2 and 53 (48%) with neutropenia. Sixty-two patients (56%) were in complete remission.

Infections and treatment toxicity represented the main reasons for ICU admission and accounted for 55% and 40% of ICU admissions, respectively. Admission to ICU was related to GHVD in 15% of patients and to hematological disease relapse in 6% of patients. In 17 (15%) patients, reasons for ICU admission were multiple. Among the 60 patients who were admitted for infectious complications, 50 patients had monomicrobial infection and 10 patients polymicrobial infection. Infection was of bacterial origin in 33 patients, viral in 15 patients, fungal in 12 patients, and *Toxoplasma gondii* infection in 2 patients.

Median simplified acute physiology score (SAPS) II was 50 [IQR 37–64] and median SOFA score was 9 [IQR 6–11]. Sixty-one (55%) patients received invasive mechanical ventilation, 51 (46%) patients needed vasopressors, and 16 (15%) patients needed renal replacement therapy. A decision to forego life-sustaining treatments was taken for 16 (15%) patients (Table 2). 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 as follows: SAPS II (p=0.004), SOFA score at ICU admission (p=0.016), invasive mechanical ventilation ($p<0.0001$), and

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]	1 [0–2]	1 [0–3]	1 [0–2]	0.33
HCT-CI ≥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%)	
Others, *n* (%)	22 (20%)	11 (20%)	11 (20%)	
Complete remission before alloHCT, *n* (%)	59 (54%)	32 (59%)	27 (48%)	0.26
Number of treatment lines before alloHCT, median [IQR]	1 [1–2]	1 [1–2]	2 [1–2]	0.19
2 or more treatment lines before alloHCT, *n* (%)	54 (49%)	25 (46%)	29 (52%)	0.11
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
Non-haploidentical donor	81 (74%)	41 (76%)	40 (71%)	
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 (%). *p* values were obtained from the univariate analysis

ALL, acute lymphoblastic leukemia; *alloHCT*, allogeneic hematopoietic cell transplantation; *AML*, acute myeloid leukemia; *HCT-CI*, hematopoietic cell transplantation–specific comorbidity index; *MDS/MPS*, myelodysplastic syndrome/myeloproliferative syndrome

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, were less frequently in complete remission before transplantation, 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, 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) whereas time from alloHCT to ICU admission and neutropenia at ICU admission were not. Complete remission before alloHCT was not associated with hospital mortality in the univariate analysis. Moreover, in a multivariate sensitivity analysis adding complete remission before alloHCT to the initial model, sequential conditioning still tended to be associated with hospital mortality (OR=2.01 [95% CI 0.97–15.40], p=0.06), whereas complete remission before alloHCT was not (OR=0.99 [95% CI 0.03–0.46], p=0.99).

Before day 3, 8 patients died in ICU and 3 patients were discharged alive. Among the 99 patients who were still in ICU at day 3, we observed a sigmoidal relationship between evolution of organ dysfunctions, assessed by delta SOFA D3-D1 (difference between SOFA score at day 3 and day 1), and probability of in-hospital mortality (p<0.0001; Fig. 1). 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). 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

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 alloHCT to ICU (days), median [IQR]	59 [14–245]	70 [22–364]	65 [26–204]	0.53
Time from alloHCT to ICU >100 days, *n* (%)	41 (37%)	23 (43%)	18 (32%)	0.32
Complete remission at ICU admission	62 (56%)	33 (61%)	29 (52%)	0.34
Acute GVHD ≥ grade 2, *n* (%)	28 (25%)	12 (22%)	16 (29%)	0.51
Neutropenia 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
Diagnosis at ICU admission (not exclusive), *n* (%)				
Infection	60 (55%)	29 (54%)	31 (55%)	1.0
Treatment toxicity	44 (40%)	22 (41%)	22 (39%)	1.0
Acute GVHD	17 (15%)	5 (9%)	12 (21%)	0.11
Relapse	7 (6%)	4 (7%)	3 (5%)	0.71
Multiple diagnoses	17 (15%)	6 (11%)	11 (20%)	0.29
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, *n* (%)				
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 (%). *p* values were obtained from the univariate analysis

*Organ dysfunction was defined by a sequential organ failure assessment (SOFA) score ≥1 for the corresponding organ system

alloHCT, allogeneic cell transplantation; *GVHD*, graft-versus-host disease; *ICU*, intensive care unit; *SAPS II*, simplified acute physiology score II; *SOFA*, sequential organ failure assessment

0.47–0.70]) or at day 3 (AUC=0.74 [0.65–0.85]). In a multivariate model including conditioning regimen, time from alloHCT to ICU admission <100 days, neutropenia at ICU admission, and acute GVHD ≥grade 2 at ICU admission, delta SOFA D3-D1 was independently associated with in-hospital mortality (OR=1.60 [1.31–2.05], $p<0.0001$).

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 (Fig. 3A).

No difference in overall survival was observed between non-haploidentical and haploidentical alloHCT ($p=0.83$; Fig. 3B). On the contrary, a sequential conditioning regimen was independently associated with decreased overall survival (HR=1.86 [95% CI 1.05–3.31], $p=0.03$) (Fig. 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 ($p=0.0004$) (Fig. 3C; Supplemental Table 1). In multivariate analysis, other factors associated with a lower overall survival were as follows: 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], $p=0.01$), invasive 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], $p=0.001$) (Fig. 2; Supplemental Figure 2). In a multivariate sensitivity analysis adding complete remission before alloHCT to the initial model, sequential conditioning still tended to be associated with

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

	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
Invasive mechanical ventilation	8.44	3.30–23.19	<0.001

Candidates entered in the multivariate analysis were conditioning regimen; time from alloHCT to ICU <100 days; active acute GVHD ≥ grade 2 at ICU admission; neutropenia at ICU admission; vasopressors; and invasive mechanical ventilation. Only the variables with reported odds ratios were selected in the final model as adding to each other predictive information

reduced overall survival (OR=1.75 [0.92–3.13], p=0.08), whereas complete remission before alloHCT was not (OR=0.89 [0.54–1.47], p=0.66).

Discussion

This study reports the outcome of 110 consecutive alloHCT patients admitted to ICU during a recent period (2010–2017). Interestingly, our cohort included patients who received sequential conditioning regimens for active hematological malignancy (31%) and haploidentical graft recipients (26%). Whether these new procedures affect the prognosis of critically ill alloHCT recipients was not known. We found no impact of haploidentical transplantation on ICU admission rate and prognosis compared to HLA-matched grafts. A sequential conditioning regimen was independently associated with poorer short- and long-term prognosis. On the contrary, our study suggests improved overall survival among critically ill MAC and RIC patients compared to that reported in previous cohorts [7, 13, 14, 19, 28, 29, 36–40]. According to published data [7, 13, 14, 29, 36, 38–42], mechanical ventilation and persistent or worsening of organ failure at day 3 were associated with higher in-hospital mortality. We also confirmed that HCT-CI score ≥2 [12, 41], active acute GVHD ≥grade 2 [14, 43], invasive mechanical ventilation [40], and vasopressors [40] were independently associated with decreased overall survival.

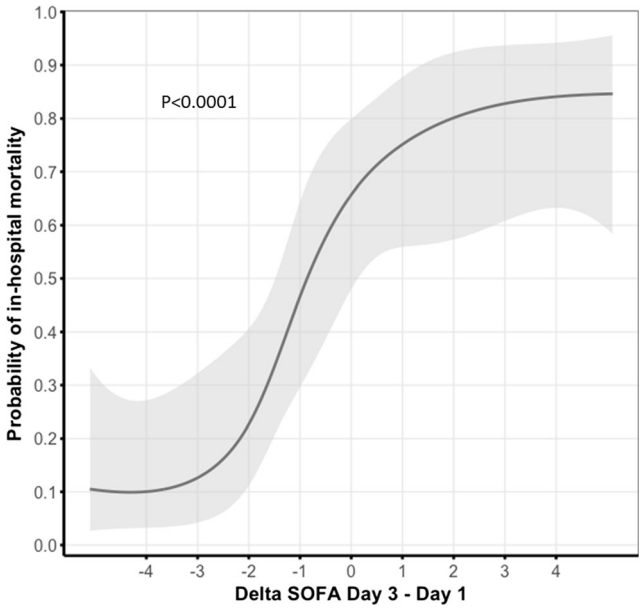


Fig. 1 Probability of in-hospital mortality according to Delta SOFA D3–D1

Over the past few years, haploidentical grafts have been increasingly used as an alternative to matched donors [3, 9]. However, the impact of this new procedure on outcome of alloHCT recipients admitted to ICU has not been addressed before. Our cohort included about one-quarter of haploidentical alloHCT recipients. Large registry-based retrospective studies have demonstrated that haploidentical alloHCT with post-transplant cyclophosphamide was associated with comparable outcomes to those of HLA-matched grafts [8, 44–46]. Consistently, we have observed similar ICU admission rates and 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 who received a sequential conditioning regimen for active disease. AlloHCT 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, while RIC regimens do not provide sufficient disease control [47]. 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 [11, 48, 49]. Only one previous cohort of critically ill alloHCT recipients has included patients who received sequential conditioning [41, 50] and its impact on outcome was not known. In our study, sequential conditioning was independently associated with increased hospital mortality whereas complete remission before alloHCT was not. 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 1 year after ICU admission. This increase in mortality could be explained by more comorbidity, higher prevalence of uncontrolled hematological malignancy, and more severe critical illness. Nevertheless, sequential conditioning remained independently associated with decreased overall survival, after adjustment for severity of critical illness and HCT-CI score and sensitivity analysis including complete remission before alloHCT procedure showed similar results.

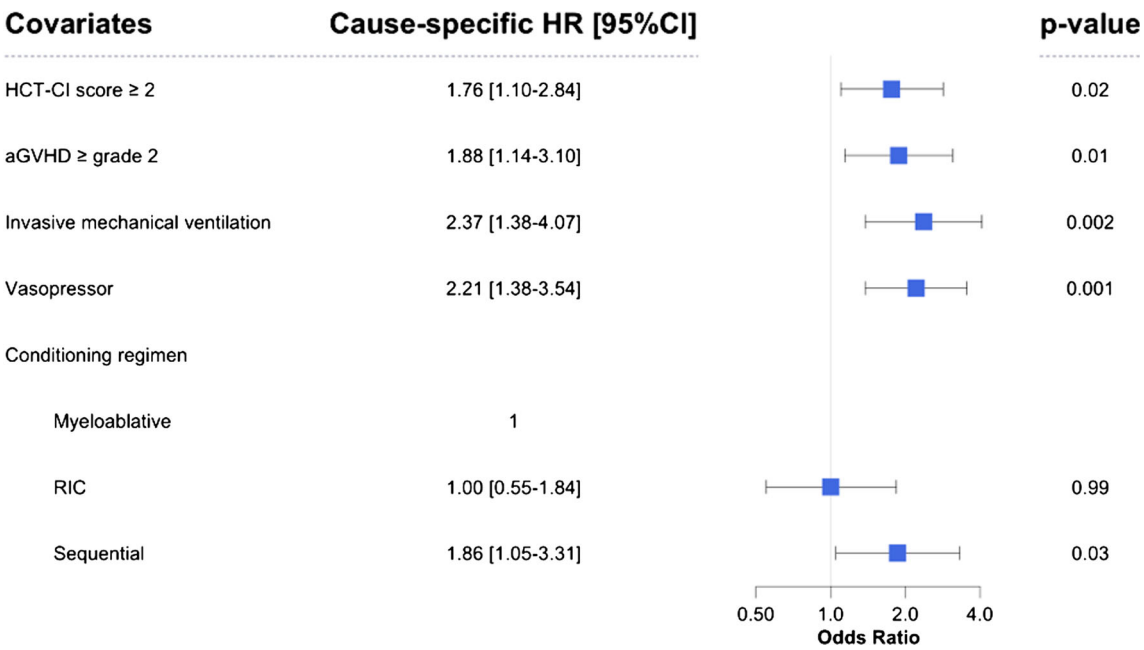
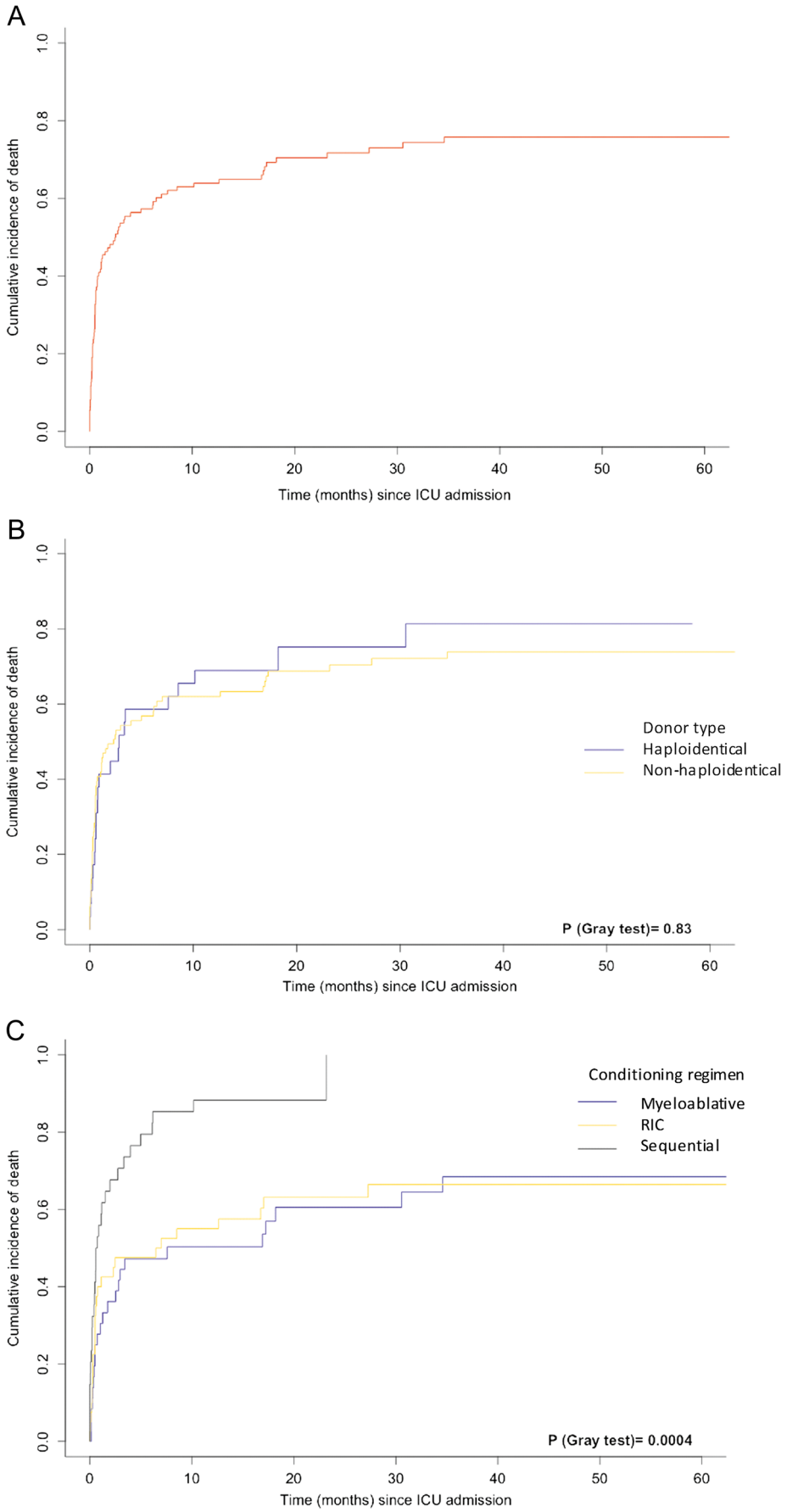


Fig. 2 Factors associated with overall survival (multivariate analysis). aGVHD, acute graft-versus-host disease; HCT-CI, hematopoietic cell transplantation–specific comorbidity index; HR, hazard ratio; CI, confidence interval; RIC, reduced-intensity conditioning. Candidates entered in the multivariate analysis were HCT-CI score ≥2; aGVHD grade ≥2; time from alloHCT to ICU >100 days; invasive mechanical ventilation; vasopressors; complete remission at ICU admission; and conditioning regimen. Only the variables with reported hazard ratios were selected in the final model as adding to each other predictive information

However, we cannot rule out the hypothesis that sequential conditioning represents a surrogate marker for increased frailty secondary to active disease and/or previous chemotherapy rather than a prognostic factor per se. Our study mainly included sequential conditioning alloHCT patients admitted to ICU for severe infectious complications and/or related to conditioning regimen toxicity which occurred in the early phase of alloHCT procedure. Our findings should not be generalized to non-critically ill sequential conditioning patients hospitalized in hematology ward and to those admitted to ICU in later time of transplantation.

Apart from sequential conditioning, mechanical ventilation was the only independent factor associated with in-hospital mortality. No other hematological characteristics, in particular neither complete remission before alloHCT nor hematological status at ICU admission, were associated with short-term prognosis. These results are consistent with previous studies [7, 13, 14, 29, 36, 38–42] 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 [50]. Platon et al. showed that the evolution of SOFA score between admission to ICU and day 3 was independently associated with ICU mortality [42]. 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 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. [38], 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 correction of organ dysfunctions is associated with better survival, (ii) an ICU time-limited 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 alloHCT patient.

We reassessed overall survival and found that 37% of alloHCT recipients were alive 1 year after admission to our ICU, which is consistent with recently reported 1-year mortality rates ranging from 61 to 87% [7, 12, 13, 36, 38–42]. 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 [7, 12, 38–40, 42] 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 1 year after admission to ICU despite similar characteristics in terms of HCT-CI score, acute GVHD, severity of critical illness, and need for invasive mechanical ventilation and vasopressors. These results corroborate ongoing improvement in long-term prognosis of critically ill MAC and RIC alloHCT patients described previously [14, 36, 39, 40]. We also confirmed that invasive mechanical ventilation [40], vasopressors [40], acute GVHD [39–41, 43], and HCT-CI ≥2 [12, 41] were


A
Cumulative incidence of death
0.0
0.2
0.4
0.6
0.8
1.0
0
10
20
30
40
50
60
Time (months) since ICU admission
B
Cumulative incidence of death
Donor type
Haploidentical
Non-haploidentical
P (Gray test)= 0.83
Time (months) since ICU admission
C
Cumulative incidence of death
Conditioning regimen
Myeloablative
RIC
Sequential
P (Gray test)= 0.0004
Time (months) since ICU admission

◀ **Fig. 3** Cumulative incidence of death among the entire cohort (**A**) and according to the donor type (**B**) and to the conditioning regimen (**C**). ICU, intensive care unit; RIC, reduced-intensity conditioning

independently associated with decreased overall survival. Interestingly, a recent study demonstrated that corticosteroid sensitivity of acute GHVD prior to ICU admission was not associated with day-90 survival. On the contrary, patients with active, stable, or worsening acute GVHD at ICU admission experienced a poorer survival [43]. In the same way, we find that acute GHVD ≥ grade 2 requiring systemic immunosuppressive treatment at ICU admission was independently associated with poor prognosis.

This study has several limitations, especially the small size of the cohort and the 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 [51]. 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.

Conclusions

The present study confirms previously known prognostic factors and provides knowledge on the impact of new alloHCT procedures on outcome of critically ill alloHCT patients. Haploidentical graft did not impact short- or long-term outcome. Sequential conditioning for active hematological disease appeared as a novel poor prognosis factor. Patients who received this conditioning regimen had a median survival of 20 days and more than 90% of them died within 1 year after ICU admission. Larger multicenter studies are warranted to confirm these results and to determine whether this unfavorable prognosis is related to the frailty of patients and/or to the toxicity of these conditioning regimens.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00277-021-04640-7.

Abbreviations AlloHCT, Allogeneic hematopoietic 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

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

Author contribution 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, OL, EB, FM, 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.

Declarations

Ethics approval and consent to participate All patients signed an anonymous data-recording consent before alloHCT 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

Competing interests FM, 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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