Improved short- and long-term outcome of allogeneic stem cell recipients admitted to the intensive care unit: a retrospective longitudinal analysis of 942 patients

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Improved short- and long-term outcome of allogeneic stem cell recipients admitted to the intensive care unit: a retrospective longitudinal analysis of 942 patients

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Abstract

Purpose: Intensive care unit (ICU) admission of allogeneic hematopoietic stem cell transplant (HSCT) recipients is associated with relatively poor outcome. Since longitudinal data on this topic remains scarce, we analyzed reasons for ICU admission as well as short- and long-term outcome of critically ill HSCT recipients.

Methods: A total of 942 consecutive adult patients were transplanted at Hannover Medical School from 2000 to 2013. Of those, 330 patients were at least admitted once to the ICU and included in this retrospective study. To analyze time-dependent improvements, we separately compared patient characteristics as well as reasons and outcome of ICU admission for the periods 2000–2006 and 2007–2013.

Results: The main reasons for ICU admission were acute respiratory failure (ARF) in 35%, severe sepsis/septic shock in 23%, and cardiac problems in 18%. ICU admission was clearly associated with shortened survival ($p < 0.001$), but survival of ICU patients after hospital discharge reached 44% up to 5 years and was comparable to that of non-ICU HSCT patients. When ICU admission periods were compared, patients were older (48 vs. 52 years; $p < 0.005$) and the percentage of ARF as leading cause for ICU admission decreased from 43% in the first to 30% in the second period. Over time ICU and hospital survival improved from 44 to 60% ($p < 0.01$) and from 26 to 43% ($p < 0.01$), respectively. The 1- and 3-year survival rate after ICU admission increased significantly from 14 to 32% and from 11 to 23% ($p < 0.01$).

Conclusions: Besides ARF and septic shock, cardiac events were especially a major reason for ICU admission. Both short- and long-term survival of critically ill HSCT patients has improved significantly in recent years, and survival of HSCT recipients discharged from hospital is not significantly affected by a former ICU stay.

Keywords: Hematopoietic stem cell transplantation, Intensive care, Outcome, Respiratory failure

Introduction

Allogeneic hematopoietic stem cell transplantation (HSCT) is increasingly used as curative treatment of malignant and non-malignant hematologic diseases [1]. Nonetheless, this therapy entails life-threatening complications, mainly because of treatment-related toxicity and opportunistic infections, leading to intensive care unit (ICU) admission in 15–40% [2–9]. In the 1980s, ICU outcome in allogeneic HSCT recipients was dismal with mortality rates up to 90% [2, 8]. However, data analysis were mostly based on small cohorts with retrospective design [2, 6, 8, 9], mixed populations including

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autologous and allogeneic transplanted patients [10, 11] and single-center experiences [2, 4, 6, 8–11].

With the introduction of reduced-intensity conditioning (RIC) and improvements in supportive care, the treatment-related mortality in HSCT patients has declined [12]. Thus, HSCT became a feasible treatment option for older patients with more comorbidities [12]. In the last 25 years, ICU survival of the general population [13] as well as the hematologic and oncologic patients improved significantly due to advances in sepsis therapy, lung protective ventilation strategies, and new anti-infective compounds [14, 15]. Although outcome of HSCT recipients remained poor [16], recent longitudinal analyses reported improvement of survival of about 20% [3, 17]. Therefore, we performed a longitudinal analysis to evaluate reasons for and outcome of ICU admission in a consecutive and homogenous cohort of critically ill HSCT recipients.

Parts from our work have been previously presented at the annual meeting of the German Cancer Congress (DKK) [18].

Take-home message

The main reason for admission to the intensive care unit for HSCT recipients remains acute respiratory failure, although it has recently declined. While short-term survival improved even in patients requiring two life-sustaining therapies, a majority of HSCT recipients should be considered for at least ICU trial support. Long-term survival of HSCT recipients after hospital discharge is encouraging and comparable to non-ICU patients.

Patients and methods

Patients

We retrospectively analyzed 942 consecutive patients who received allogeneic HSCT at Hannover Medical School, Germany, between January 2000 and December 2013. During this time period, all ICU admissions were documented. In case of multiple admissions per patient, only the first one was analyzed. At Hannover Medical School, use of vasopressors (VP), non-invasive ventilation (NIV) and invasive mechanical ventilation (IMV), renal replacement therapy (RRT) or other extracorporeal therapies are restricted to the ICU and not performed in the transplant unit.

Before start of conditioning, we routinely discuss intensive care therapy, withdraw of life-sustaining therapies and do-not-resuscitate orders with the patients. In case of critically illnes allogeneic stem cell recipients will be reviewed by both, the attending hematologist and intensivist, selected for at least an ICU trial and admitted to the internal ICU with highest standards and abundant experience in handling immunocompromised patients.

Graft-versus-host disease (GvHD) prophylaxis consists of CyA/MMF (Cyclosporine A/Mycophenolatmofetil) in reduced intensity and CyA/MTX (Cyclosporine A/Methotrexate) in myeloablative conditioning regimen. In addition, more than three quarters of the patients received antithymocyte globulin (ATG) at a total dose of 20–60 mg/kg. Infectious prophylaxis was provided according to the recommendations of the Infectious Diseases Working Party of the German Society for Hematology and Medical Oncology (AGIHO/DGHO) and the German Working Group for Blood and Marrow Transplantation (DAG-KBT) [19].

Data collection

Data collection included demographics, hematologic disease and status, transplant-associated data as well as incidence and grade of acute and chronic GvHD [20]. Individual risk assessment was performed according to European Group of Bone and Marrow Transplantation (EBMT) risk score [21] considering age of the patient, disease status, time interval from diagnosis to transplant, donor type as well as Karnofsky performance status [22]. Patients admitted during conditioning and discharged from ICU before transplantation were not included in this study. A detailed recruiting chart is given in Fig. S1.

The following ICU-related data were collected: reasons for ICU admission, interval between HSCT and ICU admission, duration of ICU stay, occurrence of organ failures and the organ support measures. Acute respiratory failure (ARF) was defined as the need of more than 3 L/min of oxygen flow via nasal cannula. Acute kidney injury was determined according to the acute kidney injury criteria of KDIGO (Kidney Disease Improving Global Outcomes) [23]. Serum bilirubin ≥ 68 mmol/L defined liver impairment [24]. Sepsis was specified according to the 2001 SCCM/ESICM/ACCP/ATS/SIS international sepsis definition [25]. Multiple organ dysfunction syndrome (MODS) was defined as altered organ function in two or more organ systems. The last follow-up was in June 2014.

Statistical analysis

Continuous variables were reported as median and interquartile range (IQR), categorical as numbers and percentages. The Mann–Whitney U test was used to compare continuous data; a Pearson's χ^2 test was used for categorical data. Parameters with a trend for ICU admission and hospital mortality were included in the multivariate logistic regression model using forward and backward selection techniques. Overall survival was estimated using the Kaplan–Meier method. Differences between groups were calculated using a stratified log-rank test. Hazard ratios for ICU mortality over time were

calculated as a time-dependent variable using a Cox proportional regression model.

All statistical tests were two-sided with a required significance level of less than 0.05. Statistical analysis was performed using SPSS 23.0 software (IBM) and R-Project software (version 3.2.3 for Linux).

Results

Patient characteristics

After transplantation, 330 out of 942 (35%) patients were admitted to the ICU. Some of the patients (17%) were initially admitted to ICUs other than the medical ICU, but subsequently transferred. The main characteristics of the total cohort and the subgroups analyzed (ICU- vs. non-ICU) are shown in Table 1. Median age at time of transplantation was 50 years (range 17–72 years) with 57% male patients. Main hematopoietic diseases were myeloid [acute myeloid leukemia (AML), myelodysplastic syndrome (MDS); 55%), lymphoid [acute lymphoblastic leukemia (ALL), lymphoma, chronic lymphatic leukemia (CLL); 22%] and myeloproliferative malignancies [myeloproliferative neoplasm (MPN), chronic myeloid leukemia (CML); 14%]. Some of the patients (26%) were transplanted in relapse. Conditioning regimen was myeloablative in 39%. Hematopoietic stem cell grafts were peripheral blood stem cells (PBSC) in 88%; donor type was matched in 80%. The underlying hematopoietic malignancy was not associated with ICU admission (ns).

Age, gender, source of graft and conditioning regimen were not significantly different between ICU- and non-ICU patients. By contrast, a mismatched donor, reduced Karnofsky performance status at time of transplantation

Table 1 Baseline characteristics

	All ($n=942$)	ICU ($n=330$)	Non-ICU ($n=612$)	p value (univariate)	p value (multivariate)
Age at time of HSCT, median (IQR)	50.0 (37–58)	51.0 (36–59)	49.0 (38–58)	0.667	
Male patients, *n* (%)	539 (57.2)	187 (56.7)	352 (57.5)	0.855	
Underlying disease, *n* (%)				0.407	
AML/MDS	517 (54.9)	170 (51.5)	347 (56.7)		
Lymphoid diseases	205 (21.8)	79 (23.9)	126 (20.6)		
CML/MPN	130 (13.8)	46 (13.9)	84 (13.7)		
Multiple myeloma	44 (4.7)	16 (4.8)	28 (4.6)		
Aplastic anemia	27 (2.9)	6 (1.8)	21 (3.4)		
Other	19 (2.0)	13 (3.9)	6 (1.0)		
Disease in remission at HSCT, *n* (%)	458 (48.6)	149 (45.2)	309 (50.5)	0.135	
Months between ID and HSCT, median (IQR)	9 (4–25)	11 (5–28)	9 (4–24)	0.036	
No. of allogeneic HSCT, *n* (%)				0.067	
1	909 (96.5)	313 (94.8)	596 (97.4)		
≥ 2	33 (3.5)	17 (5.2)	16 (2.6)		
Karnofsky scoring at transplantation, *n* (%)				0.005	0.005
≥ 80%	890 (94.5)	302 (91.5)	588 (96.1)		
< 80%	52 (5.5)	28 (8.5)	24 (3.9)		
Donor type, *n* (%)				0.022	0.021
Matched	756 (80.3)	251 (76.1)	505 (82.5)		
Mismatched	186 (19.7)	79 (23.9)	107 (17.5)		
Source of stem cells, *n* (%)				0.162	
PBSC	829 (88.1)	286 (86.7)	543 (88.7)		
Bone marrow	103 (10.9)	38 (11.5)	65 (10.6)		
Cord blood	9 (0.9)	6 (1.8)	3 (0.5)		
PBSC + bone marrow	1 (0.1)	0 (0.0)	1 (0.2)		
Conditioning regime, *n* (%)				0.554	
Myeloablative	367 (39.0)	124 (37.6)	243 (39.7)		
RIC	575 (61.0)	206 (62.4)	369 (60.3)		

AML acute myeloid leukemia, *CML* chronic myeloid leukemia, *EBMT* European Society for Blood and Marrow Transplantation, *HSCT* hematopoietic stem cell transplantation, *ICU* intensive care unit, *ID* initial diagnosis, *MDS* myelodysplastic syndrome, *MPN* myeloproliferative neoplasm, *PBSC* peripheral blood stem cells, *RIC* reduced intensity conditioning

and time between initial diagnosis and HSCT were associated with ICU admission. Multivariate analysis revealed that mismatched donor and reduced Karnofsky performance status significantly correlated with ICU admission (Table 1).

ICU admission

Median time between HSCT and ICU admission was 77 (16–300) days. The main reasons were ARF in 35% ($n=105$), severe sepsis in 23% ($n=70$) and cardiac events (dysrhythmia, decompensation, infarction) in 18% ($n=53$). Other reasons like acute kidney injury, bleeding, and impaired consciousness occurred in 14% ($n=42$). Admission after emergency surgery was seen in 7% ($n=20$) and GvHD led to ICU admission in 3% ($n=10$) of patients. Patients admitted the to ICU after scheduled surgery or after diagnostic procedures were excluded from analysis ($n=30$). In order to display the complexity and multifactorial etiology for ICU admission, both reasons for admission and concomitant organ dysfunctions during ICU stay were plotted in Fig. 1.

Median time between HSCT and ICU transfer was related to the reason for ICU admission (Fig. S2). Patients with cardiac events, respiratory failure, severe sepsis or GvHD required intensive care early after 21 (7–102), 69 (17–226), 73 (11–249) and 93 (60–157) days post-HSCT. respectively (all ns). In contrast, patients with emergency surgery were admitted after 341 days (44–1131, $p<0.01$). Overall length of ICU stay was 4 days (2–10) and significantly different in survivors and non-survivors (3 vs. 6 days; $p<0.01$). Depending on the main reason for admission, the median duration was 3 (2–5) days for patients with cardiac events, 3.5 (2–12) days after emergency surgery and 4 (2–8) days in patients with severe sepsis. However, patients with respiratory failure or GvHD stayed significantly longer with a median duration of 6 days (2–13) and 6.5 days (2–15), respectively ($p=0.001$).

Organ dysfunctions

During ICU stay, ARF occurred in 77% of the patients ($n=232$). In half of these patients (50%, $n=116$), ARF was caused by extra-pulmonary conditions [e.g. cardiogenic pulmonary edema, extrapulmonary sepsis resulting in acute respiratory distress syndrome (ARDS)]. NIV was used as the primary approach in 39% of the patients

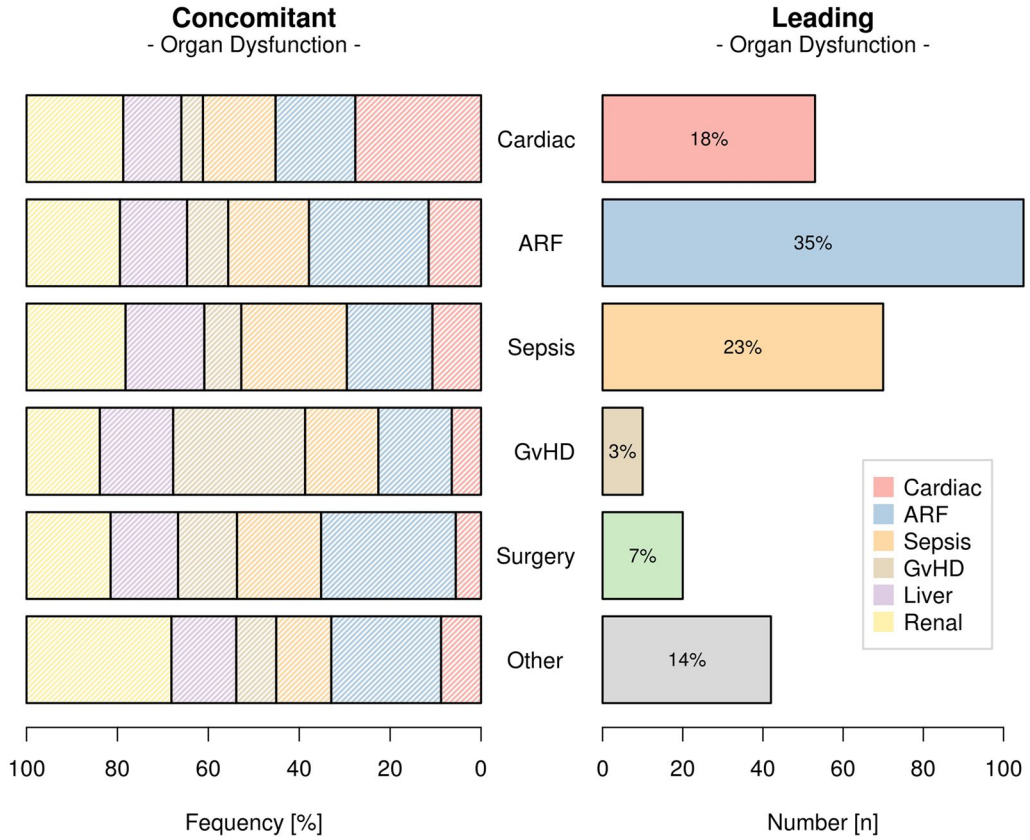

Fig. 1 Organ dysfunctions

($n=91$), with NIV failure requiring secondary intubation in 60% ($n=55$) of those. IMV was used in 65% of the patients with ARF ($n=154$) with a median ventilation time of 4 (2–12) days.

Cardiac events occurred in 47% of the patients ($n=139$). In detail, 26% ($n=78$) suffered from dysrhythmia, 16% ($n=48$) from cardiac failure and 2% ($n=7$) from acute coronary syndrome.

Treatment with VP was necessary in 63% of the patients ($n=190$), mainly due to septic shock, which occurred in 47% ($n=142$). Gram-positive bacteria were isolated in 23% ($n=65$), Gram-negative bacteria in 13% ($n=36$) and both types of bacteria in 7% ($n=20$). Fungal infections occurred in 21% ($n=60$) and viral infections in 26% ($n=69$) of the patients.

A total of 75% ($n=223$) of the patients suffered from acute kidney injury and RRT was initiated in half of those. Median duration of RRT was 4.5 days (2–11). MODS occurred in 83% of the patients ($n=249$). Some of the patients (16%, $n=48$) already had a recurrent or progressive hematologic disease after HSCT when admitted to ICU.

Short-term and long-term survival

Median follow-up from HSCT for all patients was 68 months. Admission to ICU was clearly associated with shorter survival ($p<0.001$): In ICU patients 1-, 3- and 5-year survival rates were 38, 22 and 18%, respectively. Patients who did not require ICU admission showed 1-, 3- and 5-year survival rates of 78, 65 and 60%, respectively (Fig. 2a).

To determine the impact of ICU on survival in a time-dependent manner, a Cox proportional hazard ratio model was built to predict mortality rates for each day from the day after HSCT. While impact of ICU admission on mortality was quite strongly predictive for the early period after transplantation (13.5-fold), a significant decreased predictive power was found in patients admitted later than day 100 (2.2-fold, $p<0.05$; Fig. 3).

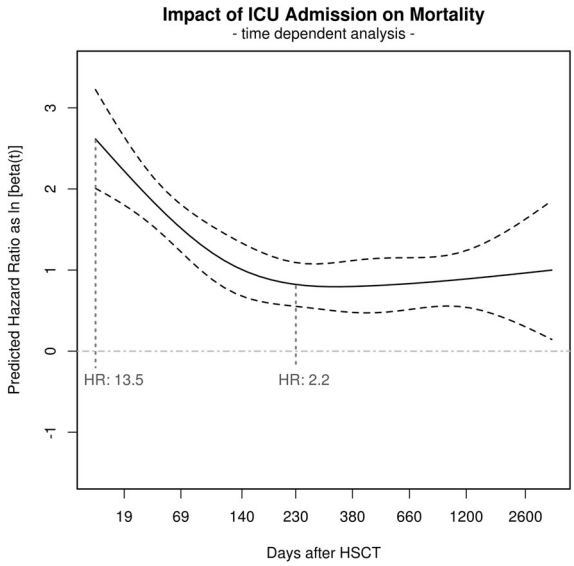

Fig. 3 Time-dependent analysis

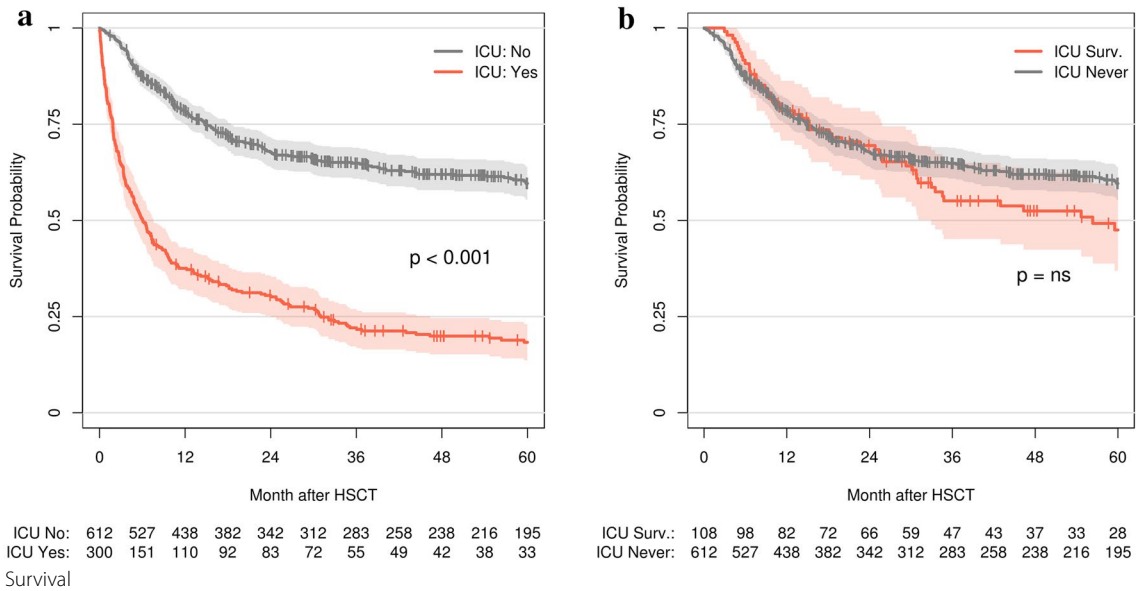

Fig. 2 Survival

For the short-term survival of critically ill HSCT recipients, both the main cause of admission as well as the therapeutic interventions were relevant: ARF, sepsis and cardiac events were associated with ICU survival rates of 38, 47 and 68%, respectively. The use of IMV, VP and RRT correlated with a significant decrease in ICU survival rates to 23, 34 and 28%, respectively ($p < 0.001$). A multivariate analysis for ICU survival as response variable revealed significance for IMV, RRT and simplified acute physiology score (SAPS II). A reduced Karnofsky performance status at time of HSCT, use of IMV as life-sustaining therapy and SAPS II were significantly associated with hospital mortality in multivariate analysis.

In summary, these data showed ICU, hospital and 1-year survival rates after ICU admission of 54, 36 and 25%, respectively. Remarkably, the post-discharge survival of ICU patients was comparable with survival of non-ICU patients at 5 years (48 vs. 60%, ns; Fig. 2b).

Graft-versus-host disease

Acute GvHD occurred in 47% ($n = 422$) of the patients, but itself did not correlate with ICU admission or ICU mortality. While mortality during ICU stay was not affected by the occurrence of GvHD, ICU survivors with acute GvHD presented a higher hospital mortality rate (27 vs. 73%, $p < 0.01$). This finding was independent of the severity of GvHD or response to corticosteroids (Table 2).

Changes over time

To identify differences or improvements over time, the study group was split into two cohorts: ICU admission from 2000 to 2006 ($n = 117$) vs. 2007–2013 ($n = 183$). Patient characteristics, data on ICU admission and stay for each group are listed in Table 2. Comparing the first and second period, patients were transplanted at an older median age, earlier after initial diagnosis and with a better Karnofsky performance status during the second period. Longitudinal analysis revealed a significant drop in ARF (43 to 30%, $p < 0.05$), whereas other causes for ICU admission did not change over time. Patients with active acute GvHD were admitted less frequently (24 vs. 14%, $p < 0.05$). The severity of illness at time of ICU admission measured by SAPS II and APACHE II as well as the incidence of life-sustaining therapies (LST) remained stable over time (Table 2). However, for each LST (MV, VP or RRT), hospital mortality decreased by an average of 15 percentage points (Fig. S3). Especially in patients requiring one or two LST, survival improved by about 25 percentage points. (Fig. S4). The multivariate analysis revealed that only the use of LST in both cohorts was significantly correlated with hospital mortality.

Over time, ICU and hospital survival increased from 44 to 60% ($p < 0.01$) and from 26 to 43% ($p < 0.01$), respectively. The 1-, 3- and 5-year survival rates after ICU admission increased significantly from 14 to 32%, from 11 to 23% and from 10 to 18%, respectively ($p < 0.01$; Table 2).

Discussion

To our knowledge, we here report the largest consecutive single-center cohort of allogeneic HSCT recipients admitted to the ICU during the post-transplant period.

Over the years, patient characteristics and reasons for ICU admission changed. ARF as the main reason for ICU admission decreased. At the same time, ICU survival significantly increased from 44 to 60%. Long-term outcome of ICU survivors was comparable to non-ICU patients.

ICU admission

Median time from HSCT to ICU admission was 77 days and therefore in-line with published data [3, 4, 9, 26]. Compared to literature, our ICU admission rate of 35% was at the upper limit [3–5, 8, 9, 17, 26]. This might be due to the low barrier strategy for ICU admission at our institution. In contrast to recent recommendations [27], 16% of the admitted patients had already experienced relapse or progression of their underlying disease with debatable indication for ICU transfer.

Organ dysfunction

Most of the published studies only reported one major reason for ICU admission. However, reality is more complex as it is mainly the combination of organ dysfunctions that is responsible for ICU admission and outcome. Therefore, we identified the main as well as concomitant reasons for admission. As shown in Fig. 1, the development of multiple organ failure occurs independently of the reason for ICU admission. For the majority of patients, the prognosis seems to be dependent on the existence of multi-organ (and not single-organ) failure when transferred to ICU (Fig. S4). These results have been confirmed by published data on the sepsis-related organ failure assessment (SOFA) score showing that two or three organ systems are frequently affected at admission [28]. However, it was crucial to determine that especially the increase of the score on day 3 in the ICU was predictive for mortality [6]. Therefore, MODS itself should not lead to primary refusal of HSCT patients as stated by Saillard et al. [29]. It is well known now that early ICU admission is associated with better outcome in hematologic–oncologic patients [16], but resources to admit every HSCT recipient with a one-organ failure to ICU are not infinitely exploitable. In case of ICU admission, a reassessment on days 3 to 5 might help to identify the patients who will not benefit from prolonged ICU support.

Table 2 Changes over time in ICU patients

Hematopoietic characteristics	2000–2006 ($n=117$)	2007–2013 ($n=183$)	p value[#]
Age at HSCT, median (IQR)	48 (34–55)	52 (39–61)	0.005
Underlying disease, *n* (%)			0.328
AML/MDS	55 (47.0)	105 (57.4)	
Lymphoid diseases	34 (29.1)	37 (20.2)	
CML/MPN	16 (13.7)	22 (12.0)	
Multiple myeloma	7 (6.0)	8 (4.4)	
Aplastic anemia	1 (0.9)	3 (1.6)	
Other	4 (3.4)	8 (4.4)	
Disease in remission at HSCT	53 (45.3)	82 (44.8)	1.000
Months between ID and HSCT, median (IQR)	14 (6–32)	8.5 (4–26)	0.021
Conditioning regime			0.002
Myeloablative	56 (47.9)	54 (29.5)	
RIC	61 (52.1)	129 (70.4)	
Donor type			0.065
Matched	95 (81.2)	130 (71.0)	
Mismatched	22 (18.8)	53 (29.0)	
Karnofsky scoring at transplantation, *n* (%)			0.004
$\geq$ 80%	99 (84.6)	174 (95.1)	
$<$ 80%	18 (15.4)	9 (4.9)	
ICU admission			
Age at ICU admission, median (IQR)	49 (35–56)	52 (41–62)	0.003
Days between HSCT to ICU, median (IQR)	56 (24–201)	77 (10–263)	0.683
Days between hospital and ICU admission, median (IQR)	18 (5–37)	14 (2–28)	0.004
Severity of illness at ICU admission			
Leukopenia, *n* (%)	32 (27.4)	73 (39.9)	0.150
SAPS II, median (IQR)	51 (38–61)	47.5 (36–63)	0.413
APACHE II, median (IQR)	22 (19–27)	21 (17–26)	0.209
Main reasons for ICU admission			
Respiratory failure, *n* (%)	50 (42.7)	55 (30.1)	0.03
Sepsis, *n* (%)	22 (18.8)	48 (26.2)	0.18
Cardiac events, *n* (%)	14 (12.0)	39 (21.3)	0.06
GvHD, *n* (%)	4 (3.4)	6 (3.3)	1.0
Emergency operative procedure	9 (7.7)	11 (6.0)	0.74
Other, *n* (%)	18 (15.4)	24 (13.1)	0.70
Life sustaining therapies			
NIV, *n* (%)	37 (31.6)	58 (31.7)	1.000
IMV, *n* (%)	61 (52.1)	72 (39.3)	0.039
Vasopressor, *n* (%)	73 (62.4)	117 (63.9)	0.887
RRT, *n* (%)	47 (40.2)	67 (36.8)	0.645
GvHD at ICU admission			0.088
No GvHD	69 (60.5)	120 (72.3)	
aGvHD	27 (23.7)	24 (14.6)	
Grade III–IV	19 (70.4)	20 (83.3)	
Steroid-refractory	11 (40.7)	16 (66.7)	
cGvHD	18 (15.8)	22 (13.3)	

Hematopoietic characteristics	2000–2006 ($n=117$)	2007–2013 ($n=183$)	p value[#]
Survival			
ICU survival (first admission)	52 (44.4)	110 (60.1)	0.009
Hospital survival	30 (25.6)	78 (42.6)	0.004
Survival after ICU admission			0.002
1-year survival	16 (13.7)	60 (32.4)	
3-year survival	13 (11.1)	47 (23.1)	

AML acute myeloid leukemia, *APACHE II* acute physiology and chronic health evaluation II, *CML* chronic myeloid leukemia, *(a/c)GvHD* (acute/chronic) graft-vs-host disease, *HSCT* hematopoietic stem cell transplantation, *ICU* intensive care unit, *ID* initial diagnosis, *IMV* invasive mechanical ventilation, *MDS* myelodysplastic syndrome, *MPN* myeloproliferative neoplasm, *NIV* non-invasive ventilation, *PBSC* peripheral blood stem cells, *RIC* reduced intensity conditioning, *RRT* renal replacement therapy, *SAPS II* simplified acute physiology score II

[#] Univariate analysis

Short- and long-term survival

ICU and hospital survival in our cohort were 54 and 36%, respectively, and therefore consistent with the reports of the most recently published studies [3, 4, 6, 17]. In line with other retrospective analyses, the initiation of NIV was not associated with higher mortality [3, 4, 26]. Other LST (IMV, VP, RRT) were related to worse outcome, as indicated by the literature [3–5, 17, 26]. We were able to show that the impact of ICU admission on mortality was highest immediately after transplantation, probably because of the high immunosuppressive level, which decreases consecutively by neutrophil engraftment, tapering of immunosuppressive therapy and immune reconstitution.

Orvain et al. described that the early mortality in the context of intensive care is particularly determined by organ failure and not by acute GvHD [30]. In our cohort, neither ICU admission nor ICU or hospital mortality correlated with acute GvHD per se. However, ICU survivors suffering from acute GvHD showed a significantly higher hospital (and long-term) mortality. This finding appears to be independent of the severity of GvHD or the response to corticosteroids.

The few studies that have evaluated long-term survival in critically ill HSCT recipients report 1-year survival rates between 16 and 33% [4–6, 9, 17, 26]. Considering only patients who were discharged alive from hospital, the reported 5-year survival rates between 43 and 51% were encouraging [17, 26]. We observed a 1-year survival rate of 25% in all patients admitted to the ICU. However, the survival rate of patients discharged from the ICU and the hospital was as high as 48% at 5 years. This survival rate was not different from patients that had never been in the ICU (Fig. 2b).

Changes over time

As observed for other critically ill patients [13], ICU survival of HSCT recipients has dramatically improved over the last decades [3, 17]. To highlight improvements over time, patients were divided into two groups admitted to ICU between 2000–2006 and between 2007–2013. The main finding was that HSCT recipients admitted to the ICU during the later time period had an improved short-term as well as long-term survival. Admission rates, time between HSCT and ICU, and reason for ICU admission did not change over time. Nevertheless, the percentage of respiratory failure as the leading cause for ICU admission dropped significantly from 43 to 30% and may explain the higher survival rate. This is in contrast to published data by Lengline et al. who described a stable rate of ARF [3]. The difference can may by attributed to four points: (A) improvement of prophylaxis and treatment for invasive aspergillosis due to use of second generation azoles; (B) a higher rate of extrapulmonary reasons for ARF (e.g. cardiogenic pulmonary edema); (C) improved fluid management on our HSCT ward avoiding toxicity due to fluid overload; and (D) more generally a better patient selection.

Previously published data showed that the majority of HSCT recipients suffering from severe GvHD did not benefit from intensive care support. As a consequence, fewer GvHD patients were transferred, which partly may explain the better ICU survival (Table 2).

Moreover, hospital mortality decreased in all patients with LST, especially in patients with 1–2 treatment modalities. Since this cannot be explained by a younger or less sick patient population, the benefits could be provided due to the improvements in general intensive care medicine in recent years. Therefore, the results already described for cancer patients with ARDS are most likely transferable to the HSCT recipients [14].

Limitations

The main limitations of our study were the retrospective design and the single-center conduct. However, to homogenize dataset and avoid potential bias due to analysis of patients after elective surgery or during conditioning therapy, these were excluded. Patients with emergency surgery as a complication of HSCT (e.g. cerebral

hemorrhage, intestinal perforation due to GvHD) were included.

Transferability of results and further developments

Admission policies vary between ICUs; therefore, our results are not transferable to other specialized centers. However, to improve data quality, we have set up a multicenter registry for critically ill hematological and oncological patients as a part of the Intensive Care in Hematological and Oncological Patients (iCHOP) network under the auspices of the German and Austrian societies for oncology, hematology and intensive care.

Conclusion

In conclusion, ICU admission of HSCT recipients was associated with a dramatic decrease in overall survival. Nevertheless, short-term survival, particularly in patients requiring 1 or 2 LST, improved during the last years. Long-term survival in hospital-discharged patients was comparable to non-ICU patients. HSCT recipients should be considered for intensive care support in terms of full code or ICU trial.

Electronic supplementary material

The online version of this article (https://doi.org/10.1007/s00134-018-5347-x) contains supplementary material, which is available to authorized users.

Abbreviations

ALL: Acute lymphoblastic leukemia; AML: Acute myeloid leukemia; APACHE II: Acute physiology and chronic health evaluation II; ARDS: Acute respiratory distress syndrome; ARF: Acute respiratory failure; CLL: Chronic lymphatic leukemia; CML: Chronic myeloid leukemia; COD: Concomitant organ dysfunction; EBMT: European Society for Blood and Marrow Transplantation; GvHD: Graft-versus-host disease; HSCT: Hematopoetic stem cell transplantation; ICU: Intensive care unit; ID: Initial diagnosis; IQR: Interquartile range; IMV: Invasive mechanical ventilation; LOD: Leading organ dysfunction; LST: Life-sustaining therapies; MDS: Myelodysplastic syndrome; MODS: Multiple organ dysfunction syndrome; MPN: Myeloproliferative neoplasm; NIV: Non-invasive ventilations; PBSC: Peripheral blood stem cells.

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Compliance with ethical standards

Informed consent and ethical approval

Informed consent for data collection was obtained from all individual participants (according to EBMT Registry forms) and approved by the local ethics committee. Our study was performed in accordance with the 1964 Declaration of Helsinki and its later amendments.

Conflicts of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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