SPECIAL ARTICLE

Trends in the outcomes of Dutch haematological patients receiving intensive care support

M. van Vliet[1]*, M.P.E.M. van der Burgt[1], W.J.F.M. van der Velden[1], J.G. van der Hoeven[2], A.F.J. de Haan[3], J.P. Donnelly[1], P. Pickkers[2], N.M.A. Blijlevens[1]

Department of [1]Haematology, [2]Intensive Care Medicine and [3]Department for Health Evidence, Radboud University Medical Center, Nijmegen, the Netherlands, *corresponding author: tel.:+31 (0)24-3615041, fax: +31(0)31-243614277, e-mail: Maarten.vanVliet@radboudumc.nl

ABSTRACT

Background: Because of the assumed dismal prognosis there is still reluctance to admit haematological patients to the intensive care unit (ICU). This study was conducted to determine trends in outcome of allogeneic haematopoietic stem cell transplant (HSCT) recipients transferred to the intensive care unit in a Dutch tertiary care hospital.

Methods: All patients who received allogeneic HSCT between 2004-2010 were included in the analyses. Baseline and outcome characteristics were compared and risk factors for ICU admission and survival were identified. Changes in outcome over time of three cohorts of HSCT recipients were investigated.

Results: Of 319 consecutive HSCT recipients, 49 (15%) were transferred to the ICU for a median (IQR) of 10 (6-45) days following their transplantation, of whom 43% were severely neutropenic and 90% had received systemic immunosuppressive therapy for graft-versus-host disease prophylaxis. Univariate logistic regression showed that transplantation from an unrelated donor and myeloablative conditioning were significant risk factors for ICU admission. Prolonged use of vasopressors, invasive mechanical ventilation and male gender were significant predictors for ICU mortality, while neutropenia and graft-versus-host disease were not. Over the years, APACHE-II severity of illness scores remained unchanged (21.0±7.1, 20.1±5.6, 21.2±6.6), while 100-day post-transplant mortality of patients who had been transferred to the ICU decreased significantly from 78% (2004/2005) to 57% (2006/2007), and 35% (2008/2009).

Conclusions: While for allogeneic HSCT patients the severity of illness on admission to the ICU did not change, the 100-day post-transplant survival improved. These data indicate that reluctance to submit haematological patients to the ICU is not warranted.

KEYWORDS

Haematopoietic stem cell transplant, haematological malignancy, intensive care unit admission, risk factors, outcome

INTRODUCTION

Patients with haematological malignancies are currently treated with intensive cytotoxic therapies often culminating in an allogeneic haematopoietic stem cell transplant (HSCT). A clear reduction in transplant-related mortality (TRM) was observed between 1967-2002, mainly due to prompt administration of antibiotics at the onset of fever, better prevention of infectious complications and improved clinical care.[1-3] Life-threatening complications now occur more frequently as a result of therapy rather than the haematological disease itself.[4,5] These complications occur acutely, typically during the period of neutropenia when patients are profoundly immunocompromised,[6] or during neutropenia recovery.[7] It is inevitable that some patients will develop medical problems requiring transfer to the intensive care unit (ICU), either for close monitoring or for intensive treatment. In the past, neutropenic patients who developed organ failure were considered to have such a dismal prognosis that physicians were reluctant to even consider admitting them to an ICU.[8] Since 2002, improved outcomes for these patients have been reported, and the importance of neutropenia as a predictor for ICU mortality was debated.[9]

Respiratory insufficiency associated with sepsis is the most common indication for admission from the haematology ward to the ICU.[5] Approximately one in four HSCT recipients require endotracheal intubation and mechanical

ventilation for acute respiratory failure.[10] Severe sepsis and septic shock are the most frequently observed reason for ICU admission.[9]

The outcome of those patients who need critical care appears to have improved,[11] although in the subgroup of HSCT recipients receiving mechanical ventilation the reported mortality rate still exceeds 80%[12] and acute graft-versus-host disease (aGvHD) is reported to be an independent predictor for death, specifically in combination with mechanical ventilation.[10] Early initiation of non-invasive ventilation is associated with significant reductions in the rates of endotracheal intubation and serious complications and an improved likelihood of survival until hospital discharge.[13] These results led to improved awareness of the benefits of early admission to an ICU, resulting in more allogeneic stem cell transplant recipients being transferred to the ICU. Nevertheless, also in the Netherlands, important differences between centres concerning ICU admission policies exist and more evidence is needed to show that ICU treatment of this specific transplant group is not futile.

In this study we investigated the changes in outcome over time of three cohorts of HSCT recipients and compared the outcome of those that needed intensive care treatment to those who did not.

DESIGN AND METHODS

Design

The records of all consecutive patients admitted to the Department of Haematology of Radboud University Medical Center, a tertiary academic hospital, between 1 January 2004 and 1 January 2010, were retrospectively analysed. HSCT recipients were identified and only their first unplanned referral to the ICU (<100 days) was included in the study. An unplanned admission was defined as an admission because of acute deterioration and not for scheduled activities that needed intensive monitoring (e.g. broncho-alveolar lavage with non-invasive ventilation support). Demographic data as well as relevant haematological data including underlying disease, donor type, type of transplant and presence of GvHD were retrieved from electronic patient files. Risk scores for TRM developed by the European Group for Blood and Marrow Transplantation (EBMT) were calculated.[14] Clinical data during ICU admission and discharge, the reason for admission, the severity of illness during the first 24 hours, as well as three outcome measures namely, mortality, and the length of ICU admission and hospital stay were collected. The severity of illness on admission to the ICU was determined by indicators of organ failure and the APACHE II score.[15] The type and duration of mechanical ventilation, renal replacement therapy and vasopressor use were extracted from the medical records. The study has been carried out in the Netherlands in accordance with the applicable rules concerning the review of research ethics committees and informed consent.

Treatment protocol

The myeloablative (MA) conditioning regimen consisted mainly of high-dose cyclophosphamide with either idarubicin when a sibling donor was available or antithymocyte globulin (ATG) when the donor was unrelated, with or without total body irradiation. The non-myeloablative (NMA) conditioning regimen consisted mainly of cyclophosphamide and fludarabine, completed with ATG in case of an unrelated donor. ATG was added to the conditioning regimen to attain T lymphocyte depletion to prevent GvHD. During the study period the method of preparation and composition of the stem cell product did not change. Patients did not receive haematopoietic growth factors and anti-microbial prophylaxis consisted of 500 mg ciprofloxacin given twice daily and 500 mg valaciclovir given three times daily. Fluconazole was given at 200 mg a day only to those who were colonised with *Candida albicans*. Vital signs (temperature, heart rate, blood pressure, respiration rate, oxygen saturation) were monitored at least four times daily with an overnight control being included during severe neutropenia to avoid any delay in starting broad-spectrum antibacterial therapy at the onset of fever.[16] Empirical therapy was started once the axillary temperature equalled or exceeded 38.5°C.

ICU transfer criteria

No explicit ICU admission policy was adopted. The decision to admit a patient to one of the level 3 general ICUs of our hospital was made by the senior haematologist and the senior intensivist.

Statistical analysis

Continuous variables were summarised using mean values and standard deviations (SD) or median values and interquartile range (IQR) if data were not normally distributed. To compare characteristics we applied the independent *t*-test for continuous variables and chi-squared or Fisher's exact tests in case of percentages. Univariate logistic regression analyses were used to identify factors associated with ICU admission and ICU mortality. The power of this study was inadequate to perform multivariate analyses.

Two-tailed p-values <0.05 were considered to indicate statistical significance. A hundred days post-HSCT survival was presented in a Kaplan-Meier curve comparing the three periods using the log-rank test. All statistical analyses were carried out with SPSS version 18.0.

RESULTS

ICU-group characteristics

Between 1 January 2004 and 1 January 2010, 319 patients received an allogeneic HSCT, of whom 49 patients were transferred to the ICU for a median (IQR) of 10 (6-45) days following their transplantation. The most common underlying diagnoses were acute myeloid leukaemia (n=14, 29%), non-Hodgkin's lymphoma (n=10, 20%) and myelodysplastic syndrome (n=8, 16%). The depth of compromised immunity at the moment of ICU transfer was emphasised by the fact that 43% of the patients were severely neutropenic (neutrophil count of ≤0.5 x 10^9/l) on ICU admission and 90% had received systemic immunosuppressive therapy for GvHD prophylaxis. Infectious complications were the main reason for ICU admission (86%), with respiratory insufficiency reported as the main symptom (67%), followed by haemodynamic instability, sepsis and septic shock. Mortality rates at 100-days post-HSCT were significantly higher for the patients who required an ICU admission (53 versus 8% in HSCT patients who did not need intensive care, p<0.01). Length of stay in the hospital was significantly longer (median 45 days; range 36-70) for patients requiring an ICU admission compared with those without ICU admission (29 days; range 23-39); p<0.01.

Risk factors for ICU admission

The characteristics of ICU patients were compared with those without intensive care treatment. Age and gender were distributed equally in both groups (*table 1*). Univariate analysis identified two haematological risk factors for ICU admission to be significant: an unrelated donor graft (OR=2.5, 95% CI 1.3-4.6) and MA conditioning (OR=2.3, 95% CI 1.1-4.7). The power of this study was inadequate to perform a multivariate analysis. The onset of aGvHD grade 2-4 within 100 days for those admitted to the ICU was 29% (14/49), similar to those not admitted to the ICU (30%).

Changes in ICU characteristics over the years

There were no changes in the number of days from HSCT to ICU admission (median 10, IQR 6-45 days after HSCT), length of ICU stay (median 4, IQR 1-12 days) or time post-ICU to hospital discharge (median 15, IQR 1-35 days) over time, nor did the APACHE II severity of illness on ICU admission and EBMT estimated risk of not surviving for five years change during the study period (*table 2*). The proportion of patients requiring endotracheal intubation

Table 1. *Demographic factors associated with ICU admission before 100 days post-HSCT (2004-2009, n=319)*

	HSCT-recipients without ICU admission (n=270)	HSCT-recipients with ICU admission (n=49)	P-value	OR (95% CI)
Age (years)	48.2 (± 11.0)	47.4 (± 11.3)	0.64[a]	
Male gender	167 (62%)	29 (59%)	0.75[b]	
Unrelated donor	89 (33%)	27 (55%)	<0.01[b]	2.5 (1.3-4.6)
Myeloablative conditioning	162 (60%)	38 (78%)	0.02[b]	2.3 (1.1-4.7)
EBMT estimated risk (n=237/43)			0.54[c]	
Low	1 (0%)	0 0%		
Intermediate	63 (27%)	14 (33%)		
High	173 (73%)	29 (67%)		

Data are expressed as mean (± standard deviation) or n with (%); [a]independent T-test; [b]Chi²-test; [c]Fisher's exact test.

Table 2. *Demographics, ICU characteristics and outcome of patients transferred to an ICU within 100 days post-HSCT in two-year periods (n=49)*

	2004/2005 (n=9)	2006/2007 (n=23)	2008/2009 (n=17)
Age	46.3 (±11.5)	47.6 (±10.3)	47.8 (±13.2)
APACHE II on admission	21.0 (±7.1)	20.1 (±5.6)	21.2 (±6.6)
EBMT estimated risk	4.0 (±1.0)	3.6 (±1.4)	2.8 (±1.1)
Invasive ventilation (days)	0.4 [0-11.3]	1.5 [0-15.5]	1.3 [0-6.3]
Non-invasive ventilation (days)	0.0 [0-0.02]	0.3 [0-1.0]	0.2 [0-0.8]
Vasopressor use (days)	0.2 [0.0-3.9]	0.4 [0.0-3.0]	0.0 [0.0-1.4]
ICU mortality	4 (44%)	8 (35%)	4 (24%)
Hospital mortality	7 (78%)	12 (52%)	7 (41%)
100 day post HSCT mortality	7 (78%)	13 (57%)	6 (35%)

Data are expressed as mean (± standard deviation), median [IQR] or n with (%).

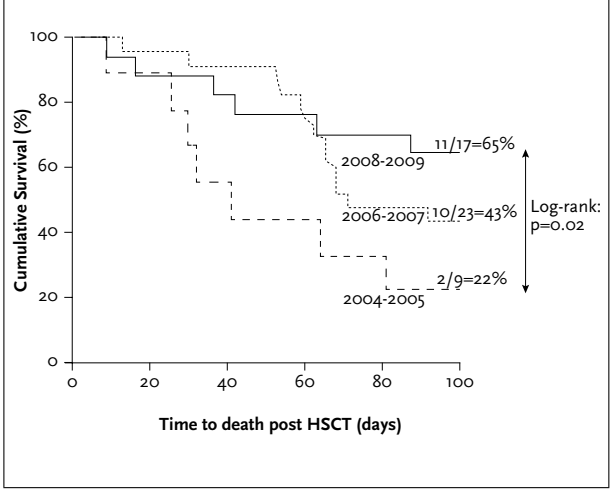
tended to decrease, but this did not reach statistical significance. In contrast, the number of non-invasive ventilation days increased (p=0.02). The number of days that vasopressor medication was required remained unchanged.

ICU mortality was 44% (2004/2005) to 35% (2006/2007) and 24% (2008/2009) and hospital mortality 78% to 52% and 41%, but these trends did not reach statistical significance. *Figure 1* illustrates the decrease in the 100-day post-HSCT mortality for patients who had been admitted to the ICU (p=0.02). A similar decrease was found for patients given MA conditioning (78% to 56% and 36%, respectively) and NMA conditioning (no patients in first period, 60% and 33% in period 2 and 3, respectively). While these improvements did not reach statistical significance, likely due to a type 2 error, they do illustrate that in both groups a comparable improvement in outcome is observed over time. The 100-day post-transplant mortality of the complete group of patients (n=319) remained constant over time between 15-19%.

Factors associated with ICU survival

Characteristics were compared between ICU survivors and non-survivors to determine the factors that were associated with survival of the patients who needed an ICU admission (*table 3*). Age and HSCT-related characteristics including donor type, bacteraemia, neutropenia and EBMT estimated risk score were similar in both groups. The duration that vasopressor medication was required (p<0.01), the number of days invasive ventilation was required (p<0.01) and male gender (p=0.04) were significant univariate predictors for ICU mortality. The APACHE II score (p=0.07) and receipt of MA conditioning (p=0.08) also tended to be related to ICU mortality. Neutropenia and both the presence of aGvHD grade 2-4 on ICU admission and the onset of aGvHD within 10- days post-HSCT were not shown to be risk factors for ICU survival.

Figure 1. *Kaplan-Meier survival curve until 100 days post-HSCT for patients with an ICU admission (n=49)*



DISCUSSION

The present study shows that the proportion of HSCT patients admitted to the ICU during the last decade has risen. Receiving stem cells from an unrelated donor and MA conditioning were shown to be the major risk factors for ICU admission as one in four required ICU admission. While their disease severity on ICU admission, as determined by APACHE-II, remained similar, the 100-day transplant-related mortality decreased. Factors associated with ICU mortality were duration of vasopressor therapy, invasive mechanical ventilation and male gender. No correlation was found between the presence of neutropenia or GvHD and the risk for ICU admission or ICU mortality. ICU and post-ICU hospital mortality was low in our population compared with recent literature.[17,18] Improved outcome for HSCT recipients might be explained by the fact that ICU treatment in general has improved, as is illustrated by higher ICU survival rates for the general adult ICU population[19] as well as in our own hospital. In addition, haematologists are more aware of the fact that admission to the ICU is feasible and effective, provided it is arranged at an early stage of deterioration. Nevertheless, APACHE-II scores during the study period did not decrease. While this cannot be deduced from our data, we have the impression that attitudes changed over time from 'no patient to be transferred to the ICU, unless....' to 'if needed, every patient should be transferred to the ICU, unless...'. Some authors propose that 'unlimited ICU treatment for a limited period', with full ICU support for e.g. four days and re-evaluation on day 5 could be an appropriate strategy of care for those patients with an unknown disease status or disease recurrence with available treatment options.[20] Our data show that 39% of the 100-day survivors needed six days or more on the ICU with a range for ICU survivors of 1-50 ICU days, implying that a decision about futility of treatment cannot be made within 4-6 days. Long-term physical, mental and social consequences of prolonged ICU admission and the effects of more extensive use of mechanical ventilation are now being studied in larger populations to determine the long-term effects of ICU treatment.

The finding that the duration of invasive mechanical ventilation and duration of vasopressor use predict ICU mortality is not surprising or new. It is well known that respiratory failure that requires mechanical ventilation and vasopressors indicates sepsis and shock and predicts mortality in almost all patient populations. Several studies have reported the use of mechanical ventilation

Table 3. *Demographic, haematological and ICU risk factors for ICU mortality (2004-2009, n=49)*

	ICU survivors (n=33)		ICU non-survivors (n=16)		P-value	OR (95% CI)
Demographics						
Age	47	(±12)	48	(±11)	0.77[a]	
Male gender	16	(49%)	13	(81%)	0.04[d]	0.2 (0.1-0.9)
Haematological parameters						
EBMT estimated risk (n=43):					1.00[d]	
Intermediate	10	(35%)	4	(29%)		
High	19	(66%)	10	(71%)		
Myeloablative conditioning	23	(70%)	15	(94%)	0.08[d]	0.2 (0.0-1.3)
Unrelated donor	17	(51%)	10	(62%)	0.47[b]	
Bacteraemia on admission (n=42)	6/27	(22%)	6/15	(40%)	0.29[d]	
Neutropenia on admission (n=40)	10/27	(37%)	7/13	(54%)	0.31[b]	
GvHD on ICU admission	2	(6%)	2	(13%)	0.59[d]	
GvHD <day 100	10	(30%)	4	(25%)	1.00[d]	
ICU parameters						
APACHE II on admission	19.6	(± 5.7)	22.9	(± 6.5)	0.07[a]	1.1 (1.0-1.2)
Invasive ventilation (days)	0.0	[0.0-5.1]	7.9	[1.6-23.7]	<0.01[c]	1.0 (1.0-1.1)
Non-invasive ventilation (days)	0.2	[0.0-0.7]	0.1	[0.0-0.3]	0.68[c]	
Vasopressor use (days)	0.0	[0.0-0.7]	2.4	[0.6-5.1]	<0.01[c]	1.5 (1.1-2.0)

Data are expressed as mean (± standard deviation), median [IQR] or proportions with (n); [a]independent T-test; [b]Chi²-test; [c]Mann-Whitney-U test; [d]Fisher's exact test.

in this profoundly immunocompromised population to be predictive for ICU mortality[21] and this is supported by the high mortality rates reported.[22] In our study population the use of non-invasive ventilation increased, relative to invasive ventilation over the years, and probably contributed to the better survival rates. However, prolonged use of non-invasive ventilation is still controversial.[23]

The benefit of organ support in patients with late-onset complications related to aGvHD and high-dose corticosteroid treatment is contentious.[24] GvHD is regarded a poor prognostic factor for the critically ill HSCT recipient.[10,12] It is remarkable that we found no indication that GvHD was related to ICU admission, nor ICU mortality. However, with the use of partially T-cell depleted grafts the overall incidence of GvHD was modest and the incidence of severe and refractory aGvHD was low. So, at least in this context, there should be no restrictions imposed on transferring these patients to an ICU when indicated.

As most ICU indications are associated with an infectious cause, haematology wards should optimise their procedures for early recognition and adequate treatment of infectious complications and their haemodynamic sequelae.[25] ICU survival seems importantly related to the extent of organ dysfunction,[26] so employing monitoring systems such as vital signs based early warning scores to recognise acute clinical deterioration[11,18] should be encouraged. Clearly, guidelines are needed to help haematologists decide when to transfer a patient to the ICU. As long as no explicit criteria for admission to the ICU are available, early consultation of intensive care physicians might improve accessibility to the ICU at an early stage of deterioration. The APACHE II might also help as it provides a clear indication of the severity of illness once the patient is admitted to the ICU even though it has not been validated for patients with haematological malignancies nor for HSCT recipients.[27,28]

Several limitations of our study need to be addressed. Obviously, caution is required as our study was retrospective in nature and the cohorts were relatively small in size. The absence of statistical significance of some endpoints, for example influence of MA/NMA conditioning on ICU mortality, is likely the result of limited power. Nevertheless, we were able to show an effect on clinically relevant outcome measures using a homogeneous cohort of haematological patients. The decrease in ICU and post-ICU hospital mortality did not reach statistical significance, possibly due to the limited power of the study. However, the impact of this decrease over time is relevant and shows better survival rates of HSCTpatients requiring ICU treatment. In addition, the increased use of NMA regimens may be a confounder as the number of patients with NMA conditioning increased simultaneously with the observed decrease in mortality. Nevertheless, the reduction in mortality was similar for both patients given MA and NMA conditioning, indicating that the type of conditioning regimen is unlikely to explain the observed improvement in survival.

CONCLUSIONS

In line with general medical ICU patients, outcomes appear to have improved for allogeneic HSCT recipients who required intensive care treatment. Neutropenia and aGvHD were not associated with ICU survival. It appears plausible that an early transfer to the ICU could further improve short- and long-term survival. ICU admittance criteria and guidelines for early transfer to the ICU should be developed.

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