Peer reviewed article

Intensive care unit admission in patients with haematological disease: incidence, outcome and prognostic factors

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Summary

Objectives: To examine incidence and outcome of intensive care unit (ICU) admission in patients with haematological malignancy and analyse prognostic factors associated with outcome.

Design: Retrospective cohort study in an intensive care unit of a tertiary referral center.

Patients: 78 patients with severe haematological malignancy were admitted 97 times between 1990–97 to the medical ICU for septic shock (18), respiratory failure (30), postoperative monitoring (19), cardiovascular (10), and central nervous complications (8), or for other reasons (12). Median age was 43 (4–73) years, average duration of ICU stay was 4 (1–43) days. Forty-two patients required mechanical ventilation, 46 vasopressors and 8 haemodialysis.

Results: Rates of ICU admission differed by treatment of the underlying disease. There were 18, 10 and 27 ICU admission per 100 treatments in patients undergoing chemotherapy for acute leukaemia, autologous and allogeneic stem cell transplantation ($p < 0.005$) respectively.

Thirty-two of 78 patients died within 60 days of ICU admission. Organ failure, i.e. cardiovascular failure requiring vasopressors, respiratory failure requiring mechanical ventilation and renal failure, requiring haemodialysis, was most significantly associated with outcome. Mortality by day 60 after admission was 16%, 36%, 64%, and 83% ($p < 0.0002$) for patients without organ failure, and for patients with 1, 2 or 3 failing organs. In a multivariate logistical regression model, only the organ failure score ($p < 0.0005$) and evidence of liver damage, defined as ASAT or ALAT >100 IU/L ($p < 0.007$), but not age, sex, primary disease and treatment of the underlying disease predicted outcome.

Conclusion: Multi-organ failure and evidence of liver damage but no other patient, disease, or treatment related factor predict outcome in patients with haematological disease admitted to the ICU.

Keywords: haematological malignancy; leukaemia; haematopoetic stem cell transplantation; intensive care unit; organ failure; outcome

Introduction

Severe haematological disease is associated with considerable disease- and treatment-related morbidity and mortality. The use of intensive chemotherapy and haematopoetic stem cell transplantation (HSCT) has increased treatment-related complications. Transferring a severely ill patient to the intensive care unit (ICU) for life support is often a difficult decision [1, 2]. Several studies have analysed outcome of ICU admission in patients with haematological malignancy [3–28]. The most difficult decision is, whether to initiate mechanical ventilation to treat respiratory failure [3–5], especially if due to interstitial pneumonitis [6], and some authors have advocated limiting intensive care in patients after HSCT based on reports of high mortality and in view of restricted resources [1, 4, 7, 8]. However, recent reports have shown improved survival of patients after HSCT requiring intensive care [8, 9]. This study reviews incidence and outcome of ICU admission of patients with severe haematological disease in a single center and analyses prognostic importance of patient, disease and treatment-related factors.

No financial support declared

Patients and methods

Patients

Seventy-eight patients with severe haematological disease, admitted to the medical intensive care unit (ICU) of the Basel University Hospital between 1990 and 1997 were analysed retrospectively. Patients with the following diagnoses were included: acute myeloid or lymphoblastic leukaemia, chronic myeloid leukaemia, lymphoma, multiple myeloma, aplastic anaemia or drug induced agranulocytosis. Charts were reviewed for a number of patient, disease, treatment and admission characteristics shown in table 1. Median age was 42 (range 4–73) years. Forty-seven (60%) were male. Most (N = 58) patients had leukaemia. Disease subclassification and disease stage are shown in table 1.

Table 1

Patient and admission characteristics.

Patient characteristics (N,%)	78	
Male sex (N, %)	47	60%
Age (yrs, median, range)	42	4–73
Follow-up (months, median, range)	27	1–90
Diagnosis		
Acute myelogenous leukaemia (N, %)	28	36%
Acute lymphoblastic leukaemia (N, %)	9	12%
Chronic myelogenous leukaemia (N, %)	14	18%
Myelodysplastic / myeloproliferative syndrome (N, %)	7	9%
Lymphoma / myeloma (N, %)	9	12%
Aplastic anaemia (N, %)	6	8%
Agranulocytosis / Other (N, %)	5	6%
Disease stage		
Initial diagnosis (N, %)	13	17%
1st complete remission / 1st chronic phase (N, %)	25	32%
More advanced disease (N, %)	20	26%
Other / not applicable (N, %)	20	26%
ICU admissions (N,%)	97	100
Treatment or primary disease prior to ICU admission:		
At diagnosis, prior to any treatment (N, %)	8	8%
Chemotherapy (N, %)	26	27%
Autologous stem cell transplantation (N, %)	8	8%
Allogeneic stem cell transplantation (N, %)	52	54%
Other (N, %)	3	3%
Acute grade II-IV graft-versus-host disease (N/N at risk, %)	25/52	48%
Main reason for ICU admission:		
Septic shock (N, %)	18	19%
Respiratory failure (N, %)	30	31%
Postoperative monitoring (N, %)	19	20%
Cardiovascular complications (N, %)	10	10%
Central nervous system complications (N, %)	8	8%
Major bleeding (N, %)	1	1%
Miscellaneous (N, %)	11	11%
Duration of ICU admission (days, median, range)	4	1–43
Apache II Score (median, range)	18	5–45
Mechanical ventilation (N, %)	42	43%
Vasopressor use (N, %)	46	47%
Haemodialysis (N, %)	8	8%
Liver damage (ASAT or ALAT >100 IU/L)	26	28%

ICU Admissions

The 78 patients were treated in the haematology ward, which is not equipped for cardiovascular or respiratory monitoring, and were admitted 97 times to the medical ICU, comprising a respiratory (8 beds), coronary (8 beds) and intermediate care unit (12 beds). Nine patients were admitted to the ICU twice, 3 patients 3 times and 1 patient 4 times on separate occasions. Admissions were considered separate, if the patient spent at least 48 hours in the regular ward in between. Reasons for ICU admission are shown in table 1. These include septic shock (18), respiratory failure (30), postoperative monitoring, (19), cardiovascular complications (10), central nervous system complications (8), major bleeding (1), various other reasons (11). Patients were admitted for the following reasons: while receiving chemotherapy (N = 25), following autologous stem cell transplantation (N = 8), allogeneic stem cell transplantation (N = 52) or other treatment (N = 3), or with newly diagnosed haematological disease (N = 8). Median duration of ICU stay was 4 days (range 1–43). Forty-two patients (43%) required mechanical ventilation, 46 patients (47%) required vasopressor use and 8 patients (8%) required haemodialysis.

Statistical analysis

The major outcome studied was death before day 60 after ICU admission. Secondary outcomes were death in the ICU, and overall survival of this population. To compare risk factors univariately associated with outcome, the chi-squared or Fisher's exact test were used, where appropriate. In univariate analysis, variables describing multi-organ failure were most significantly associated with outcome. Therefore a simple organ failure score [29–33] adding one point for every organ failing, ie, cardiovascular failure requiring vasopressors, respiratory failure requiring mechanical ventilation and renal failure, requiring haemodialysis was used to assess the impact of multi-organ failure on outcome. A logistic regression model with forward stepwise variable entry was fitted to analyse risk of day-60 mortality adjusting for patient age, sex, disease and disease stage, treatment of underlying disease, main reason for ICU admission, organ failure score, liver damage, and Apache II scores. The Kaplan-Meier estimator was used to calculate survival probabilities of patients with specific combinations of admission characteristics and compared among groups by the log-rank test.

Results

During the observation period, (January 1990 – September 1997), 95 patients received chemotherapy for acute leukaemia, (typically 3 cycles of induction and consolidation treatment were given), and 82 autologous and 193 allogeneic stem cell transplants were done. The ICU admission rates per 100 treatments were 18/100 for chemotherapy, 10/100 for autologous and 27/100 for allogeneic stem cell transplants (p <0.005).

Figure 1

Day 60 mortality by number and type of organ failing, expressed as number of deaths per number of patients observed.

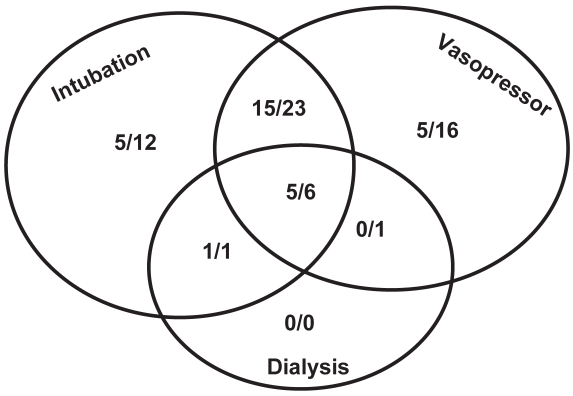
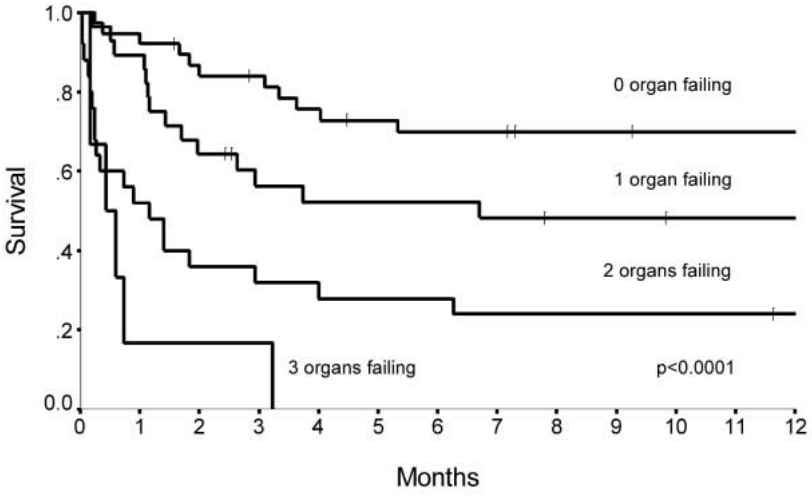


Figure 2

One year survival probabilities after ICU admission with 0, 1, 2, 3 failing organs.



Thirty-two of the 78 (41%) patients died within 60 days of ICU admission, 20 (26%) died in the ICU. Thirty-seven of 97 admissions were followed by death within 60 days because of repeated admissions during this period. As shown in table 2, factors significantly associated with death before day 60 were vasopressor use and mechanical ventilation. Haemodialysis, evidence of liver damage (defined as ASAT or ALAT >100 IU/L) and Apache II scores were of borderline significance only. The reason for ICU admission was strongly correlated with death; patients admitted for septicaemia and respiratory failure had a much higher mortality than patients admitted for all other reasons combined. The underlying disease, type of treatment (ie, chemotherapy, autologous or allogeneic HSCT), presence or absence of graft-versus-host disease (GvHD), patient age and sex were not significantly associated with outcome. The organ failure score, adding a point for vasopressor use, mechanical ventilation and haemodialysis, had high prognostic significance. Day 60 mortality was 16%, 36%, 64%, and 83% (p <0.0002) and ICU mortality was 0%, 7%, 52%, and 83% (p <0.00001) for patients without organ failure, and for patients with 1, 2 or 3 failing organs. In a multivariate logistic regression model, risks of death (± 95% confidence interval) by day 60 were 1.0; 5.0 (1.3–86.8); 20.1 (4.7–86.8); and 25.1 (2.0–317.5) for patients with 0, 1, 2, or 3 organs failing (p <0.0005). The only other variable significantly associated with death at day 60 was evidence of liver damage defined as ASAT or ALAT >100 IU/L (relative risk 5.5 (1.61–18.48), P = 0.007). The underlying disease, prior treatment, presence or absence of GvHD, age, sex, and Apache II score, were not significantly associated with day 60 mortality risk in this model once the organ failure score was adjusted for.

A graphical representation of the association of organ failure with risk of death at 60 days is shown in figure 1. Figure 2 shows the one year survival probability after admission to ICU with 0, 1, 2, and 3 organs failing. Survival probabilities were 70 ± 15% (95% confidence interval) after admission with 0 organ failing (N = 38), 48 ± 19% with 1 organ failing (N = 28), 24 ± 17% with 2 organs failing (N = 25), and 0% with 3 organs failing (N = 6) (p <0.0001). The probability of long-term survival (at 3 years) after ICU admission was 41 ± 12% (95% confidence interval) for the entire cohort.

Table 2

Univariate outcomes.

	death day 60			death in ICU		
	N/N eval	**%**	**p**	**N/N eval**	**%**	**p**
Vasopressor use			0.002			0.0001
Yes	25/46	54%		19/46	41%	
No	12/51	23%		1/51	2%	
Mechanical ventilation			0.0001			0.0001
Yes	26/42	62%		19/42	45%	
No	11/55	20%		1/55	2%	
Haemodialysis			0.03			0.003
Yes	6/8	75%		5/ 8	62%	
No	31/89	35%		15/89	17%	
Liver damage			0.04			0.59
present	14/26	54%		6/26	23%	
absent	20/66	30%		12/66	18%	
Apache II Score			0.03			0.04
>18	22/46	48%		13/46	28%	
<18	11/46	26%		5/46	11%	
Age			0.99			0.86
>40 yrs	21/55	38%		11/55	20%	
≤40 yrs	16/42	38%		9/42	21%	
acute GvHD			0.53			0.07
grade 0–I	12/27	44%		9/27	33%	
grade II–IV	9/25	36%		3/25	12%	
Indication for admission			0.003			0.001
Sepsis	8/18	44%		5/18	28%	
Respiratory failure	18/30	60%		12/30	40%	
Other	11/49	22%		3/49	6%	
Prior treatment			0.60			0.81
Pretreatment	3/8	38%		2/ 8	25%	
Chemotherapy	11/26	42%		4/26	15%	
Autologous SCT	2/ 8	25%		2/ 8	25%	
Allogeneic SCT	21/52	40%		12/52	23%	
Other	0/ 3	0%		0/ 3	0%	
Disease			0.49			0.99
Acute leukaemia	17/46	37%		10/46	24%	
CML	9/18	50%		3/18	17%	
MDS/MPS	5/10	50%		2/10	20%	
Lymphoma/myeloma	3/11	27%		2/11	18%	
Aplastic anaemia	1/6	17%		1/6	17%	
Agranulocytosis / other	4/9	44%		2/9	22%	
Duration of ICU stay			0.37			0.08
≤7 days	26/73	36%		12/73	16%	
>7 days	11/24	46%		8/24	33%	
Duration of ventilation			0.53			0.76
≤4 days	12/21	57%		9/21	43%	
>4 days	14/21	67%		10/21	48%	
Organ failure score			0.0002			0.0001
0 organ failing	6/38	16%		0/38	0%	
1 organ failing	10/28	36%		2/28	7%	
2 organs failing	16/25	64%		13/25	52%	
3 organs failing	5/ 6	83%		5/ 6	83%	

Discussion

This retrospective cohort study, analysing a heterogeneous population of patients with severe haematological disease admitted to the ICU showed that organ failure status, but not patient- and disease-related factors such as primary diagnosis, stage of disease, type of treatment, presence or absence of acute GvHD, age and sex, were significantly associated with survival. Other factors significantly related with mortality in univariate analysis were reason for admission, such as septicaemia and respiratory failure; evidence of liver damage, and the Apache II composite score. In multivariate analysis, only the cumulative number of failing organs (organ failure score) including the cardiovascular system necessitating vasopressors, the respiratory system requiring mechanical ventilation and the kidney, requiring dialysis and elevated transaminases were significantly associated with the probability of death by day 60. The reason for ICU admission and the Apache II composite score were highly correlated with organ failure status ($p < 0.0001$) and were therefore not independent prognostic factors. The rather large number of patients admitted for postoperative monitoring is due to our policy of aggressive excision of invasive pulmonary fungal lesions [34] in neutropenic patients.

The most difficult decision about ICU admission of patients with haematological disease is whether to intubate and mechanically ventilate a patient. As patients are suffering from a potentially terminal illness, end of life decisions become important. If certain combinations of disease- and treatment-related factors and the presentation at the time of ICU admission were indicative of imminent death, prolongation of suffering could be avoided. Unfortunately we were not able to identify these patients over and above organ failure status, the very reason for most ICU admissions. The organ failure score did not differ much, whether it was applied to patients, known to be at very high risk, ie, recipients of allogeneic stem cell transplants, or other patients. Among patients after allogeneic stem cell transplantation, and even among those with graft-versus-host-disease, there were some ventilated patients surviving. One year survival differed considerably whether patients had single or multiple organ failure on admission, but only the small group with more than 2 organs failing had zero survival.

Several studies have addressed outcome of patients with haematological disease admitted to the ICU [3–28]. The rationale for ICU admission is often discussed and strategies to maximise survival are weighed against limiting unnecessary suffering and costs [7]. Surviving patients may return to a life of good quality [10]. Many studies attempted to identify prognostic factors at the time of ICU admission, to guide clinicians and patients in decision making about intensity of treatment. Several patient- and disease- related factors have been shown to be associated with poor survival: age [4, 11] although cut-off levels varied; type of disease [12]; disease stage, remission status and response to chemotherapy [3, 11, 13]; stem cell transplantation including donor type [3,14,15], time interval between stem cell transplantation and ICU admission (> versus <90 days) [4], grade of acute GvHD [16]; and degree and duration of neutropenia [3, 13, 16–18]. Some of these factors were however not predictive of adverse outcome in other reports [7, 9, 18–22]. ICU admission characteristics significantly associated with survival were: reason for intubation [16, 19, 23], mechanical ventilation to treat pulmonary failure rather than to treat severe mucositis, or postoperative states; multi-organ failure [7–10, 20, 24]; Apache II/III scores [2, 8, 9, 24]. Duration of mechanical ventilation [4, 16, 18, 25], and of ICU treatment [16, 18, 25] was significantly associated with adverse outcome in some studies. In a large case control study in HSCT patients [8] there were no survivors among an estimated 398 patients who had lung injury and vasopressor support or sustained hepatic and renal failure. As shown in figure 1 some patients in this present series survived multiple organ failure states, however patient populations might not be comparable across studies.

Treatment of the underlying disease was not significantly associated with outcome, but with the incidence of ICU admission. Recipients of allogeneic HSCT (27%) were more likely to be admitted to the ICU than patients undergoing autologous stem cell transplantation (10%) or chemotherapy (18%). Other studies quoted figures in the 7–23% range [2, 9] for transplant patients. This wide range can be explained by different equipment for patient monitoring in haematology wards and most certainly by different criteria for ICU admission among centers.

This study has several limitations: it is retrospective, with a small and heterogeneous patient population. The retrospective nature of this study might bias the estimates as criteria for interventions might differ in different patient groups. The rather liberal ICU admission criteria led to inclusion of patients with good prognosis. This is exemplified by the overall survival rate of 41% at 3 years, contrasting with lower survival probabilities in other reports of 3–24% [12, 16, 23–27]. Next to organ failure status no other variable was significantly associated with outcome. Factors identified in other studies such as allogeneic HSCT [15], presence of GvHD, advanced or uncontrolled disease or higher age were not significantly associated with outcome. This could be explained by small numbers of patients lacking statistical power to detect a difference but also by patient selection, ie, patients with uncontrolled haematological malignancy or graft versus host disease were not admit-

ted to the ICU but rather received palliative care in the haematology ward, thus making them unobservable for this study. Last, it is biologically plausible, that once disease has progressed to the stage of organ failure, the latter becomes prognostically more important than the factors leading to it.

We conclude, that in this study of 97 ICU admissions of patients with severe haematological disease, the organ failure status at the time of ICU admission but no other patient- disease- or treatment related factors were significantly associated with short term and long term survival. Multiorgan failure remains the most difficult problem in these patients.

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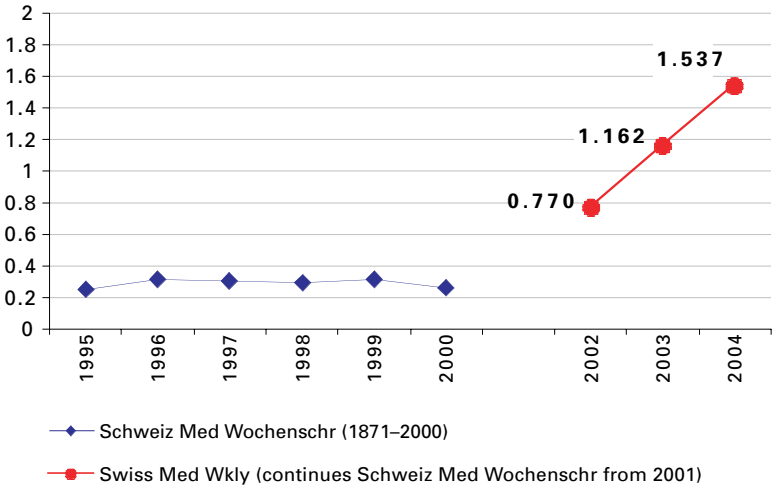

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