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Impact of critical care reconfiguration and track-and-trigger outreach team intervention on outcomes of haematology patients requiring intensive care admission

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Abstract Patients with haematological disorders have previously been considered to have poor outcomes following admission to intensive care units. Although a number of haematology centres from outside the UK have now demonstrated improved outcomes, the continuing perception of poor outcomes in this patient group continues to adversely affect their chances of being admitted to some intensive care units (ICUs). Over the past 10 years, there have been many advances within the disciplines of both haematology and intensive care medicine. This study was done to assess outcomes and the impact of an early warning scoring system (EWS) and early involvement of ICU outreach teams. One hundred five haematology patients (haematopoietic stem cell transplant (HSCT) or non-HSCT) had 114 admissions to ICU between April 2006 and August 2008 which coincided with hospital-wide implementation of EWS. The survival to ICU discharge was 56 (53%). Thirty-three (33%) patients were alive at 6 months giving a 1-year survival of 31%. Of the 39 HSCT patients, nine were post-autologous and 30 post-allogeneic transplant. The survival to ICU discharge was 22 (56%) with 14 (36%) patients alive at 6 months. One year survival was 36%. Prior to the introduction of EWS and critical care outreach team (2004), survival to ICU discharge was 44% which has

increased to 53% (2006–2008). This is despite an increase in mechanical ventilation in 2006–2008 (50%) as compared to 2004 (32%). The improvement in ICU survivorship was even more prominent in HSCT patients (37% in 2004 versus 56% in 2006–2008). There was a trend towards decreasing Acute Physiology and Chronic Health Evaluation scores with time, suggesting appropriate patients being identified earlier and having timely escalation of their treatment.

Keywords Haematological malignancy · Intensive care unit · Early warning score

Introduction

Patients with haematological disorders requiring haematopoietic stem cell transplant (HSCT) or non-HSCT treatments have previously been considered to have poor outcomes following admission to intensive care units. Poor outcomes have particularly been associated with patients who have had HSCT (especially with myeloablative conditioning) [1–3] and patients who required mechanical ventilation [4–6]. Although a number of haematology centres from outside the UK have now demonstrated improved outcomes in patients requiring intensive care unit (ICU) support [7, 8], the continuing perception of poor outcomes in this patient group may continue to adversely affect their chances of being admitted to some ICUs.

Over the past 10 years, there have been many advances within the disciplines of both haematology and intensive care medicine, which may improve patient outcomes, including those aimed at providing early identification of patients who are clinically deteriorating or at risk of deterioration using track-and-trigger systems (such as Early

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Warning Scores (EWS)), and earlier involvement of ICU staff, for example using critical care outreach teams. A recent review of outcomes of a large number of haematology patients requiring ICU in UK is relatively lacking especially after all these advances in ICU care.

We have undertaken a retrospective analysis of haematology patients who required admission to an ICU or high dependency unit (HDU) facility within a UK teaching hospital with a large department of clinical haematology and stem cell transplantation. Data has been analysed before and after the introduction of an EWS system, critical outreach nursing and continuous consultant intensive care physician cover for HDU patients, in order to assess the impact of these changes on patient outcomes in terms of escalation of therapy and survival.

Methods

A retrospective analysis was performed of 105 patients with haematological malignancies (HSCT or non-HSCT) admitted to the ICU at Nottingham University Hospital (City Campus) between April 2006 to August 2008. The ICU is a 16-bed mixed-dependency ICU caring for both levels 2 (HDU) and 3 (ICU) patients and staffed by consultant intensive care physicians, sharing responsibility of care with the admitting physicians. Prior to 2005, the hospital operated separate HDU and ICUs with HDU patients cared for by their home teams. There has been no expansion in absolute numbers of critical care beds during the period of the study. In 2005, an EWS system with outreach-team involvement was extended to haematology wards in order to identify patients at risk of deterioration. Using the EWS protocol, patients identified as reaching a preset trigger led to a review by an outreach team consisting of specialist ICU nurses to assess whether ICU admission was required or whether further support could be provided within the ward environment. Patients continued to be monitored by the outreach team until their EWS score had either fallen to below the preset trigger or they were transferred to the ICU. Standard EWS cutoffs were applied to all patients.

The protocol using EWS and outreach teams (Table 1) in haematology wards was applied to all inpatients. EWS score was based on pulse, blood pressure, respiratory rate, temperature, central nervous system function and urine output recorded every 6 h. For each parameter, an abnormal observation would score 0 to 3 depending upon the degree of abnormally high or low reading. All the points were added to give a total EWS score. If this score was <3 , observations were continued every 6 hourly. If the score was 3, hourly observations and EWS scoring were done. If the score remained at 3 for 4 h, medic on the ward was informed to review the patient and to institute appropriate

management. If the EWS reached 4 or more, ICU outreach team was informed to review the patient in addition to the medic on the ward. Outreach team would then monitor patient hourly and also set up high flow oxygen, if needed, until EWS score is back down to less than 4 with treatment or, otherwise, inform the ICU physicians, if EWS continued to deteriorate, for transfer of patient to ICU after their review. The purpose was neither to transfer patients too late when they were already extremely unwell nor too early when they could be managed on the wards with close liaison with ICU outreach team.

Data was collected by reviewing case notes, computer patient records and an Acute Physiology and Chronic Health Evaluation (APACHE2) database. Data collected included patient demographic data, disease, disease status at time of admission, treatment (whether HSCT or Non-HSCT), reason of ICU admission, number of organ failures (cardiovascular failure, respiratory failure, renal failure, gastrointestinal dysfunction, haematological failure, liver failure, neurological dysfunction), septic status, need for inotropic support, non-invasive ventilation, mechanical ventilation and renal replacement therapy (continuous veno-venous haemofiltration or haemodialysis). Cardiovascular failure was defined as patients with clinical and echocardiogram proven cardiac failure or arrhythmias, respiratory failure as hypoxia requiring oxygen therapy, moderate and severe renal failure if estimated glomerular filtration rate was 30–59 and <29 ml/min/1.73 m², respectively, haematological failure if neutrophils were $<1 \times 10^9/l$ and moderate to severe liver failure if bilirubin or liver enzymes were greater than twice of upper normal limit.

In addition, the requirement of patients for specific levels of intervention was recorded, where level 2 support is that required for single organ failure; for example, inotropes or non-invasive ventilation; and level 3 support is defined as the support of multiple organs, or endotracheal intubation and mechanical ventilation alone (typically HDU care is considered level 2 and ICU level 3).

ICU survival and survival to discharge from hospital were recorded as was survival and disease status at 6 months. For HSCT patients, type of transplant (related or unrelated), intensity of conditioning (myeloablative or non-myeloablative), days post-transplantation at the time of ICU admission, presence or absence of graft-versus-host disease and steroid use were also recorded.

Data was analysed to assess proportion of patients discharged from ICU and from the hospital, proportion of patients alive at 6 months and their disease status (CR, PR, disease relapse/progression) and overall survival. Overall survival was calculated from ICU admission until death or censor at date of analysis. Univariate and multivariate analysis of variables for overall survival was done using Graphpad Prism and SPSS.

Table 1 Early warning scoring and outreach involvement protocol

EWS score	3	2	1	0	1	2	3
RR	<8			9–14	15–20	21–29	>29
HR	<40	41–50		51–100	101–110	111–129	>129
Temperature	<35			35–38.4		38.5–39	>39
Systolic BP	<80	81–90	91–100	101–199			>199
CNS				alert	voice	pain	unconscious
Estimated hourly urine		<0.5 ml/kg	<1 ml/kg	1–2.5 ml/kg		>3 ml/kg	

If score=4 or more → contact: doctor to review within 30 min and critical outreach → hourly observation and EWS scoring

If score=3 → hourly observation and scoring → score=3 for next 4 h → contact doctor → doctor review within 30 min → score=3 for further 2 h → contact doctor and critical outreach → continue hourly observation and scoring

Similar data was collected and analysed for haematology patients admitted to ICU in 2004, which provided us with a pre-EWS group of patients for comparison.

Results

The patient characteristics are shown in Table 2. In the 28 months analysed in the time period 2006–2008, there were a total of 114 haematology admissions to critical care which involved 105 patients. In 2004, there were 29 admissions involving 27 patients. This represents an increase in admissions from 2.4 to 4.1 admissions per month. The median age of patients in 2006–2008 was 60 years compared with 57 in 2004. In 2006–2008, 66 patients (63%) were non-HSCT patients; in the 2004 period, 11 patients (41%) were non-HSCT.

The majority of non-HSCT patients in both groups, approximately 70%, either suffered from acute leukaemia or non-Hodgkin's lymphoma. In 2006–2008 group, there was an increase in newly diagnosed patients who were already critically ill at the time of admission (seven patients, 11% of non-HSCT patients, compared with none in 2004). During 2004, proportionally more non-HSCT admissions were for patients becoming critically ill after their first course of chemotherapy (54% versus 10%).

There was a slight variation in the proportions of patients with advanced disease who were admitted to ICU in both time periods (36% in 2004, 27% in 2006–2008). These patients were mostly transferred with limitations to intensive support already agreed, with the ceiling of treatment usually being non-invasive ventilation; do-not-attempt-resuscitation orders were commonly in place.

There was a proportional reduction in patients admitted after HSCT (59% in 2004, 37% in 2006–2008 group), with half of these admissions occurring within 3 months of transplantation in 2004 and 35% in 2006–2008 group. Most HSCT patients were in complete or partial remission at the time of admission. During 2006–2008, nine out of 39

transplant patients were post-autologous HSC transplant, and 30 were post-allogeneic transplant. Out of the 30 allogeneic transplant recipients, 16 had non-myeloablative, and 14 had myeloablative conditioning. Most of the patients had received peripheral blood stem cells. Between 30% and 40% of patients in both groups were suffering from graft versus host disease and were on immunosuppressants and steroids.

The main reasons for requiring critical care support were respiratory failure secondary to chest infection, or sepsis. Other causes are listed in Table 3. The length of ICU stay varied from 0.01 to 34 days. The organs which were affected at the time of admission in 2006–2008 group of patients are shown in Table 3. The most frequent was respiratory failure (84%) followed by haematological failure (neutropenia with neutrophils $<1.0 \times 10^9/l$; 48%), moderate to severe renal failure (28%), moderate to severe liver impairment (32%), gastroenterological dysfunction (24%), cardiac failure (13%) and neurological dysfunction (14%). The percentages of different organs affected were quite similar in 2004 group, with the exception of gastroenterological dysfunction (7%) and cardiac failure (1%) which were seen lesser. The number of patients considered to have more than two organ failures was 44% in 2004 and 37% in 2006–2008, i.e. slightly lower in 2006–2008. Comparing 2004 and 2006–2008 groups, there appeared to be an increase in the use of non-invasive ventilation (29% versus 51%). A corresponding increase was also seen in the use of mechanical ventilation (32% versus 50%). More patients required renal replacement therapy during 2004 as compared to patients during 2006–2008 (19% versus 16%).

Further comparison of patients from 2004 with those from 2006–2008 showed only a slight increase in patients requiring level 3 support (51% versus 54%) although during this time, the average APACHE2 score (only available for admissions during 2007–2008) showed a decreasing trend which did not reach significance ($p=0.95$, using an unpaired t test).

Table 2 Disease characteristics of haematology patients admitted to intensive care

		2004 n=27	2006–2008 n=105
Age, median (range)		57 (22–79)	60 (17–84)
Sex (M/F)		20/7	52/53
Diagnosis			
Non-HSCT		11	66
Disease	AL	4	21
	NHL	4	25
	Other miscellaneous	3	20
Disease status	CR/PR	1	30
	Advanced	4	13
	New/1st chemotherapy	6	23
HSCT		16	39
Disease	AL	5	18
	CML	3	5
	MM/PCL	5	9
	Other miscellaneous	3	7
Disease status	CR/PR	11	29
	Relapsed/refractory disease	3	10
	NA	2	–
Transplant type	Auto	7	9
	NMA allo	6	16
	MA allo	3	14
Stem cell source	PSBC	16	35
	BM	0	4
GVHD (%)	(Allografts)	3 (33)	12 (40)
Steroids required	(Allografts)	3 (33)	11 (37)

Abbreviations: AL acute leukaemia, NHL non-Hodgkins lymphoma, CLL chronic lymphocytic leukaemia, MM multiple myeloma, AA aplastic anaemia, TTP thrombotic thrombocytopenic purpura, CML chronic myeloid leukaemia, CR complete remission, PR partial remission, SD stable disease, Auto autologous transplant, Allo allogeneic transplant, NMA non-myeloablative conditioning, MA myeloablative conditioning, PSBC peripheral blood stem cells, BM bone marrow, NA not available, GVHD graft-versus-host disease

Outcomes of these haematology patients admitted to ICU in 2004 and 2006–2008 are shown in Table 4. The median length of stay for all patients increased from 3 to 4 days, although that of level 3 patients remained relatively static throughout the time period of the study at 5 days. There was an increase in the proportion of all patients surviving to discharge from hospital, and this also was reflected in level 3 patients, including those who underwent mechanical ventilation. Only two patients who required renal replacement therapy survived to be discharged from hospital. Longer term survival at 3 and 6 months also appeared to be improved, though the trend became more modest. The median follow-up of patients who survived ICU admission and were discharged from hospital was 9 months.

A small number of patients in both groups were discharged from ICU to receive palliative care on the haematology wards.

The disease status of survivors at 6 months revealed that, in 2006–2008, 91% were in complete remission from their respective haematological conditions, and a further 6% were in partial remission. Only a small minority of 3% had already relapsed by 6 months. These results were similar to

that seen in 2004 with only one patient in each group suffering a relapse. The overall survival at 1 year of the whole cohort of patients admitted to ICU during 2006–2008 was 31% (Fig. 1).

Proportionally, more HSCT patients survived to hospital discharge and were alive at 6 months in 2006–2008. One year overall survival of HSCT patients was 36% (Fig. 1). Of these patients, 93% were in remission at 6 months. All of the HSCT patients who were alive at 6 months were also in complete remission. The only patient who relapsed also went back to complete remission after receiving donor lymphocyte infusion. HSCT patients appeared to have equally good outcomes when compared to non-HSCT patients in 2006–2008.

Univariate analysis of the following factors, age > 60 years, HSCT versus non-HSCT, disease status (CR/PR versus active disease), type of transplant (non-myeloablative versus myeloablative), greater than two organ failures, neutropenia, inotropic support, requirement of mechanical ventilation and renal support, revealed that failure of greater than two organs, neutropenia and renal support were significant factors adversely affecting survival with *p* values of 0.007, 0.02 and 0.01, respectively. On multivariate

Table 3 Intensive care admission details of haematology patients

	2004 <i>n</i> =27	2006–2008 <i>n</i> =105
Indication for admission		
Respiratory failure/pneumonia (%)	15 (56)	54 (51)
Neutropaenic sepsis (%)	8 (30)	29 (28)
Pulmonary oedema (%)	1 (4)	3 (3)
Typhlitis (%)	–	5 (5)
Seizures (%)	1 (4)	–
Post-operative (laparotomy) (%)	–	3 (3)
Organ failures		
Cardiac failure/arrhythmias (%)	1 (4)	14 (13)
Respiratory failure (%)	23 (85)	88 (84)
Renal failure (moderate/severe) (%)	8 (30)	29 (28)
Gastrointestinal dysfunction (%)	2 (7)	25 (24)
Neutropaenia (%)	13 (48)	50 (48)
Hepatic impairment (moderate/severe) (%)	10 (37)	34 (32)
Neurological dysfunction (%)	5 (19)	15 (14)
HSCT patients		
Admitted <3 months of transplant (%)	8 (50)	14 (36)
Patients requiring level 3 support (%)	14 (51)	57 (54)
APACHE2 score, mean (SD)	29.8 (9.7)	25.5 (7.4) ^a
Patients requiring mechanical ventilation (%)	8 (32)	51 (50)
Patients requiring renal replacement therapy (%)	5 (19)	16 (16)

^a APACHE2 scores were available only for patients admitted to ICU during 2007–2008

analysis, only failure of greater than two organs proved to be an independently significant factor adversely affecting survival (*p* value 0.002; Table 5).

Discussion

There have been more recent reports (2008, 2009) on outcomes of haematology patients to ICU showing improvement consistently in most. However, the indications and timing of ICU admissions is still not entirely clear. Our study suggests an improvement in outcomes following the development of an early warning system allowing for early recognition of patients at risk of deterioration, early involvement of critical care outreach teams and subsequent transfer to ICU/HDU if needed. During the time period involved, critical care was also restructured allowing for greater collaboration between intensive care physicians and haematologists.

The increase in both overall ICU admissions and patients requiring level 3 support over the time period, coupled with the trend towards decreasing average APACHE scores, suggests that appropriate patients are being identified earlier and are having their treatment escalated accordingly. During the same time period, the involvement of ICU outreach team allowed for patients to receive far higher concentrations of “high-flow” humidified oxygen and aggressive fluid resuscitation and intermittent central

venous monitoring whilst remaining on the haematology wards.

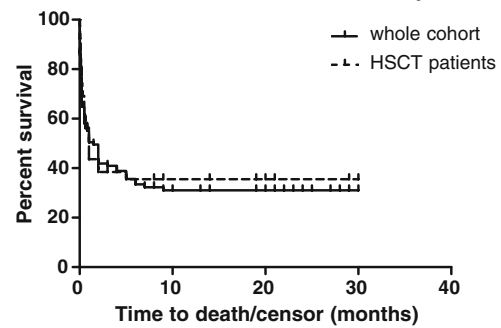
Previous studies have suggested that as many as 7% of haematology admissions for malignancy are complicated by critical illness, and 1.7% are admitted to intensive care [9]. The total number of haematology admissions to hospital during the time period (2006–2008) are not known, so it is possible that the absolute increase in level 3 ICU admissions reflects an absolute increase in hospital admissions, and that the use of critical care outreach teams masks the increase in level 2 requirement. The study confirmed the findings of other studies that good outcomes in terms of short-term and medium-term survival are possible in this cohort of patients with 53% of patients discharged from ICU back to the ward, and in 33% of patients being alive at 6 months, out of which, majority (91%) were in complete remission from their respective haematological conditions [10–12]. We also looked at the outcomes of all non-surgical patients admitted to ICU as well as hospital mortality for comparison with patients with haematological malignancies. The ICU mortality of all non-surgical patients in 2007 was 26.9%, and hospital mortality was 37.4%. Hence, although the ICU survival of haematology patients admitted to ICU was lower as compared to other non-surgical admissions, still the results were not too far off. In 2006–2008, haematology patients requiring ICU admission had a 1-year survival of 31%.

Table 4 Outcomes of haematology patients admitted to intensive care

	2004	2006–2008
All patients	<i>n</i> =27	<i>n</i> =105
Length of ICU/HDU stay in days median (range)	3 (1–21)	4 (1–34)
Survival to ICU discharge (%)	12 (44)	56 (53)
Survived to discharge from hospital (%)	10 (37)	47 (45)
Alive at 6 months (%)	8 (30)	37 (35)
Disease status at 6 months (%)		
CR	6 (75)	30 (91)
PR/SD	1 (13)	2 (6)
Relapsed	1 (13)	1 (3)
All HSCT patients	<i>n</i> =16	<i>n</i> =39
Survival to ICU discharge (%)	6 (37)	22 (56)
Survival to discharge from hospital (%)	5 (31)	16 (41)
Alive at 6 months (%)	3 (19)	14 (36)
Disease status at 6 months (% survivors)		
CR	3 (100)	12 (86)
PR/SD		1 (7)
Relapsed		1 (7)
Patients requiring level 3 care	<i>n</i> =14	<i>n</i> =57
Length of ICU/HDU stay in days median (range)	5 (1–21)	5 (1–24)
Survival to ICU discharge (%)	5 (36)	23 (40)
Survived to discharge from hospital (%)	3 (21)	18 (32)
Survived to discharge from hospital if mechanical ventilation required (%)	1 (14)	17 (33)
Survived to discharge from hospital if renal replacement therapy required (%)	0	2 (12)

Abbreviations: AL acute leukaemia, NHL non-Hodgkins lymphoma, CLL chronic lymphocytic leukaemia, MM multiple myeloma, AA aplastic anaemia, TTP thrombotic thrombocytopenic purpura, CML chronic myeloid leukaemia, CR complete remission, PR partial remission, SD stable disease, Auto autologous transplant, Allo allogeneic transplant, NMA non-myeloablative conditioning, MA myeloablative conditioning, PBSC peripheral blood stem cells, BM bone marrow, NA not available, GVHD graft-versus-host disease

Patients who were admitted to ICU after HSCT had an equally good outcome with 1-year survival of 36%. This is contrary to what has been reported previously in a number of studies in which HSCT patients had done worse as compared to non-HSCT patients [3] and confirms no difference in outcome shown in other more recently published studies [13–15]. Reduced intensity conditioning, better (high resolution) HLA tissue typing, close monitoring of cytomegalovirus (CMV) with real time quantitative PCR with treatment of CMV reactivation to prevent CMV

Survival of the whole cohort and HSCT patients**Fig. 1** One-year survival of the whole cohort and HSCT patients (2006–2008): 31% and 36%, respectively

disease and improvement in anti-bacterial and anti-fungal treatments are some factors, to mention the least, which may have improved outcomes of HSCT patients. Amongst the 39 ICU admissions of HSCT patients, there was no significant difference in outcomes of myeloablative versus non-myeloablative conditioning transplant recipients. This again is contrary to previous reports of myeloablative transplant recipients doing worse as compared to non-myeloablative conditioning.

Patients requiring mechanical ventilation did slightly worse than those not requiring mechanical ventilation, but this difference in outcome did not prove to be statistically significant on univariate as well as multivariate analysis. This is reflected in the increasing proportion of patients surviving after mechanical ventilation and conflicts with previous studies which indicate mechanical ventilation to be a marker of poor outcome [12, 16–19]. Failure of greater

Table 5 Analysis of factors affecting survival

	Univariate	Multivariate
Age <>60 years	1-year survival 32% versus 30% (<i>p</i> value 0.46)	<i>p</i> =0.90
HSCT versus non-HSCT	1-year survival 36% versus 31% (<i>p</i> value 0.20)	<i>p</i> =0.58
Type of transplant (NMA versus MA)	1-year survival 36% versus 21% (<i>p</i> value 0.57)	
Organ failure: ≤2 versus >2 organ failure	1-year survival 40% versus 14% (<i>p</i> value 0.007)	<i>p</i> =0.002
Neutropenic versus non-neutropenic	1-year survival 21% versus 40% (<i>p</i> value 0.02)	<i>p</i> =0.61
Inotropic support	1-year survival 22% versus 38% (<i>p</i> value 0.08)	<i>p</i> =0.44
MV versus no MV	1-year survival 25% versus 38% (<i>p</i> value 0.22)	<i>p</i> =0.38
Renal support	1-year survival 11% versus 37% (<i>p</i> value 0.01)	<i>p</i> =0.12
Disease status (CR/PR versus relapsed/refractory disease)	1-year survival 35% versus 21% (<i>p</i> value 0.23)	<i>p</i> =0.45

than two organs, neutropenia, renal support and inotropic support were significant factors on univariate analysis, but on multivariate analysis, only failure of greater than two organs proved to be an independently significant factor adversely affecting survival. Unfortunately, one of the limitations of this study is the relatively low sample size making multivariate analysis less reliable; however, it is reasonable to assume that late transfer to ICU once patients have already developed multiple organ failure is likely to be associated with poorer outcomes.

Although this study is limited by being retrospective in nature, and of a heterogeneous population, it suggests firstly that the outcomes of haematology patients admitted to ICU have improved and that the threshold for admission and also for instituting level 3 care decreased. This trend towards improved outcomes is also present amongst haematopoietic stem cell transplant patients. Secondly, it also suggests that the earlier involvement of critical care using EWS scoring, critical care outreach and earlier involvement of intensive care physicians has played a role in any improvement. Thirdly, in addition to the improved outcomes of patients with haematological malignancies admitted to ICU, a vast majority of these patients who survive ICU admission are in complete remission, especially the ones after HSCT, and many cured of their underlying malignancies. Hence, reluctance to admit these patients receiving intensive and potentially curative treatments to ICU on the basis of their underlying haematological malignancy is not justified.

We suggest that the recent National Institute of Clinical Excellence (NICE, UK) guidelines advocating the use of EWS or a similar trigger system for all adult hospital patients at risk of deterioration are likely to benefit hospitals involved in intensive treatments such as those required for haematology patients [20, 21].

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