Characteristics and outcomes of patients with a haematological malignancy admitted to the intensive care unit for a neurological event

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Patients with a haematological malignancy are at risk of critical events warranting admission to an intensive care unit. Bone marrow dysfunction and treatment modalities such as cytotoxic drugs and stem cell transplantation induce a prolonged immunocompromised state, which results in complications of infectious origin, with respiratory failure due to pneumonia being the most frequent reason for ICU admission.[1] Patients with a haematological malignancy are also prone to critical neurological events, including haemorrhage, infection, localisation of the haematological malignancy in the central nervous system (CNS), impaired cerebral blood flow due to leukostasis, and neurotoxicity of drugs and radiation.[2] For example, after allogeneic haematopoietic stem cell transplantation, patients were found to have an increased risk of fatal CNS bleeding.[3] Patients with non-Hodgkin lymphoma (NHL) are at risk of developing CNS involvement, which carries a poor prognosis, resulting in high-risk subsets of NHL patients being treated prophylactically with chemotherapy or radiotherapy applied to the CNS.[4] Further, specific types of drugs or high doses of drugs used in the treatment of haematological malignancies are associated with an increased seizure risk.[5]

Admission to an ICU for patients with a haematological malignancy or neurological disorder is sometimes considered futile, as prognosis is often regarded as poor,[6-8] but survival of patients with a critical neurological emergency and those with a haematological malignancy have improved over time.[9-12] This improvement is thought to reflect advances in critical care and management of the underlying disease.[13]

To our knowledge, there are no data available describing critically ill patients with a haematological malignancy admitted to the ICU for a critical neurological event. More knowledge about this distinctive population could facilitate decision making about ICU admission and treatment policies for these patients. Our aim was to assess characteristics and outcomes of neurocritically ill patients with an underlying haematological malignancy in order to improve insight into the reasons for and courses of their ICU admissions.

ABSTRACT

Objectives: Patients with haematological malignancies are at risk of concomitant critical neurological events warranting intensive care unit admission. We aimed to examine the characteristics and outcomes of this patient population, as more knowledge could facilitate decision making on ICU admission and treatment.

Design, setting and participants: A retrospective cohort study of 68 patients in adult ICUs of six Dutch university hospitals between 2003 and 2011.

Results: The median Acute Physiology and Chronic Health Evaluation (APACHE) II score was 23 (IQR, 16–27), and 77% of patients needed mechanical ventilation within the first 24 hours of admission. Forty percent of patients had received an allogeneic stem cell transplantation, and 22% were neutropenic on admission. The most frequent underlying haematological condition was non-Hodgkin lymphoma (27%). Seizures were the most common neurological event for ICU admission (29%). The median ICU length of stay was 5 days (IQR, 1–13 days). ICU mortality (28%), hospital mortality (37%) and 3-month mortality (50%) were comparable with other studies of ICU patients with haematological malignancies. Factors associated with 3-month survival were baseline platelet count (113×10^9/L in survivors v 39×10^9/L in non-survivors, $P<0.01$) and APACHE II score (20 in survivors v 25 in non-survivors, $P=0.02$).

Conclusions: Patients with a history of haematological malignancy presenting with a critical neurological event have comparable survival rates with other patients with a haematologic malignancy admitted to the ICU. Our findings suggest that restrictions in ICU care are not justified for this patient population.

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Methods

Patients

We identified adult patients with an underlying haematological malignancy, for whom the primary reason for ICU

admission was a neurological event, from local hospital registries whose data were submitted to the Dutch National Intensive Care Evaluation (NICE) between 2003 and 2011. We combined data with the hospital health care costs and utilisation databases of the six participating university hospitals. In these registries, the data that are prospectively collected for every ICU patient included demographics, presence of chronic diseases and comorbidities, reason for admission and patient outcomes. We did not need to obtain informed consent because we used de-identified registry data obtained from routine care. The NICE registry is officially registered according to the Dutch Personal Data Protection Act (2001). Patients were eligible for inclusion if the primary reason for ICU admission was a neurological condition and when a haematological malignancy was registered as a comorbidity.

Data collection and analysis

We also retrieved the following data from the patient's records: admission diagnosis, underlying haematological malignancy and presence of active haematological disease, Acute Physiology and Chronic Health Evaluation (APACHE) II score, stem cell transplantation status, and neutrophil and platelet count at ICU admission. Haematological malignancies were clustered in five categories covering the most frequent haematological diagnoses in our study: non-Hodgkin lymphoma (NHL), acute myeloid leukaemia (AML), acute lymphocytic leukaemia (ALL), multiple myeloma (MM) and other haematological malignancies. Patients with NHL were differentiated by the presence or absence of primary CNS localisation. Outcome data consisted of ICU and hospital lengths of stay (LOSs), duration of mechanical ventilation (MV), Glasgow coma scale (GCS) score at ICU discharge, and ICU, hospital and 3-month mortality. Neutropenia was defined as a neutrophil count $< 0.5 \times 10^9$/L. Baseline and outcome parameters were compared between survivors and non-survivors.

Table 1. Baseline characteristics ($N = 68$)

Characteristic	Data
General	
Mean age, years (SD)	52 (14)
Male, *n* (%)	40 (59%)
Median APACHE II score (IQR)	23 (16–27)
On mechanical ventilation within 24 hours after admission, *n* (%)	52 (77%)
Median time spent in hospital before ICU admission, days (IQR)	5 (0–23)
Median Glasgow coma scale score, (IQR)	11 (4–15)
Neurological: admission diagnosis, *n* (%)	
Seizures	20 (29%)
Intracranial haemorrhage	16 (24%)
Encephalopathy	12 (18%)
Central nervous system infection	10 (15%)
Myopathy/neuropathy	7 (10%)
Other*	3 (4%)
Haematological	
Diagnosis, *n* (%)	
Non-Hodgkin lymphoma	18 (27%)
Primary central nervous system localisation	*5 (28%)*
Acute myeloid leukaemia	13 (19%)
Acute lymphocytic leukaemia	11 (16%)
Multiple myeloma	9 (13%)
Other	17 (25%)
Previous stem cell transplantation, *n* (%)	
Autologous	3 (4%)
Allogeneic	27 (40%)
Median time between stem cell transplantation and ICU admission, months (IQR)	3.1 (0.7–7.4)
Active haematological disease, *n* (%)	32 (47%)
Neutropenia, *n* (%)	15 (22%)
Median platelet count, $\times 10^9$/L (IQR)	65 (29–194)

APACHE = Acute Physiology and Chronic Health Evaluation. IQR = interquartile range. * Ischaemic stroke and traumatic brain injury. ICU = intensive care unit.

Statistical analysis

Normally distributed continuous data are expressed using means and SDs. Non-normally distributed continuous data are expressed using medians and interquartile ranges (IQRs). Categorical data are shown as numbers and percentages. Patient groups were compared using the Fisher exact test for categorical variables, andWhitney *U* test for non-normally distributed continuous variables. The Kruskall–Wallis test was used to compare more than two non-normally distributed groups. We compared outcome characteristics of different neurological and haematological subsets of patients, and $P < 0.05$ was considered significant. We performed statistical analyses using SPSS, version 22.0 (SPSS Inc).

Results

Patient characteristics

General characteristics

In the study period, 919 first ICU admissions of patients with a haematological malignancy were registered. Sixty-

Table 2. Outcome of patients with a haematological malignancy admitted to the intensive care unit for a neurological event (*N* = 68)

Outcome	Data
Median length of stay, days (IQR)	
Hospital	35 (14–57)
ICU	5 (1–13)
Median time on mechanical ventilation, days (IQR)	3 (1–10)
Tracheostomy during ICU stay, *n* (%)	10 (15%)
Mortality, *n* (%)	
ICU	19 (28%)
Hospital	25 (37%)
At 3 months	34 (50%)

IQR = interquartile range. ICU = intensive care unit.

eight patients fulfilled the inclusion criteria, and their baseline characteristics are summarised in Table 1 and Figure 1. Most patients were men (59%), with a mean age of 52 years. Patients were severely ill, as shown by the median APACHE II score of 23 (IQR, 16–27). Over three-quarters of the patients (77%) needed MV within 24 hours of admission. Nearly one-quarter of patients had neutropenia on admission, and the median platelet count was 65$10^9$/L (IQR, 29–194 × 10^9/L).

Neurological characteristics

Most admissions were due to seizures (29%). Other frequent neurological conditions leading to ICU admission were intracranial haemorrhage (ICH) (24%) and encephalopathy (18%). The median GCS at admission was 11 (IQR, 4–15). ICH was recorded as the reason for ICU admission mostly in patients with AML (38%) or NHL (31%). The median platelet count did not differ significantly between patients with (72 × 10^9/L) and without (65 × 10^9/L) an ICH. Neurosurgical decompression was performed in half (8 of 16) of the patients with ICH. Admission due to CNS infection occurred in 10 patients, most often with NHL (30%) and MM (30%). Four of the 10 patients with CNS infection were neutropenic at ICU admission.

Haematological characteristics

The most frequent underlying haematological conditions were NHL (27%) and AML (19%). In almost one-third of NHL patients, the lymphoma was localised primarily in the CNS. Thirty patients had a history of haematopoietic stem cell transplantation (44%) performed at a median of 3 months (IQR, 0.7–7.4 months) before ICU admission. Almost half of the patients (47%) had active haematological disease at the time of ICU admission.

Outcomes

Overall outcomes and mortality

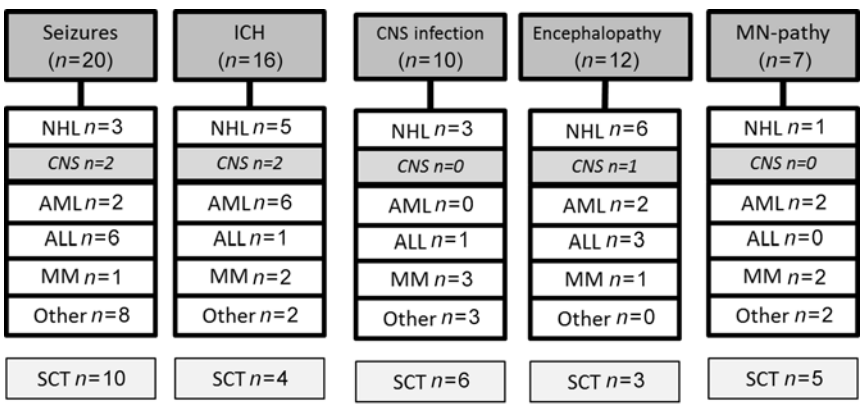
The median ICU LOS was 5 days (IQR, 1–13 days) with a median duration of MV of 3 days (IQR, 1–10 days) (Table 2). Overall, 3-month survival rate was 50%. ICU, hospital and 3-month mortality rates for the different neurocritical conditions and haematological malignancies are shown in Table 3. Overall, survivors had a higher platelet count on admission (median, 113 × 10^9/L v 39 × 10^9/L, $P = 0.008$) and lower APACHE II scores (20 v 25, $P = 0.019$) (Table 4). Other variables did not differ significantly between survivors and non-survivors.

Outcomes by neurological and haematological condition

ICU and hospital LOSs differed among the neurological conditions. The ICU LOS was longer for patients with myopathy/neuropathy (median, 43 days; IQR, 13–76 days) compared with other patients ($P < 0.001$). Although the LOS was longer, a relatively good survival was seen in these patients, with a 3-month survival rate of 71%.

Hospital and ICU LOSs and duration of MV did not differ between patients with different underlying haematological conditions. In five of the 18 patients with an NHL, the

Figure 1. Overview of neurological events warranting intensive care unit admission, categorised by underlying haematological malignancy



ICH = intracranial haemorrhage. CNS = central nervous system. MN-pathy = myopathy and neuropathy. NHL = non-Hodgkin lymphoma. *CNS* = central nervous system localisation of NHL. AML = acute myeloid leukaemia. ALL = acute lymphocytic leukaemia. MM = multiple myeloma. SCT = haematopoietic stem cell transplantation.

Table 3. Mortality rates of patients, by neurological event and haematological malignancy, *n/N* (%)

Diagnosis	Mortality rate		
	ICU	Hospital	3-month
Neurological event			
Seizures	2/20 (10%)	4/20 (20%)	8/20 (40%)
Intracranial haemorrhage	7/16 (44%)	8/16 (50%)	9/16 (56%)
Encephalopathy	3/12 (25%)	5/12 (42%)	7/12 (58%)
CNS infection	3/10 (30%)	4/10 (40%)	5/10 (50%)
Myopathy/neuropathy	1/7 (14%)	1/7 (14%)	2/7 (29%)
Other	3/3 (100%)	3/3 (100%)	3/3 (100%)
Haematological malignancy			
Non-Hodgkin lymphoma	3/18 (17%)	5/18 (28%)	10/18 (56%)
Primary CNS localisation	0/5 (0%)	0/5 (0%)	2/5 (40%)
No primary CNS localisation	3/12 (25%)	4/12 (33%)	7/12 (58%)
Acute myeloid leukaemia	6/13 (46%)	7/13 (54%)	7/13 (54%)
Acute lymphocytic leukaemia	2/11 (18%)	2/11 (18%)	6/11 (55%)
Multiple myeloma	4/9 (44%)	4/9 (44%)	4/9 (44%)
Other	4/17 (24%)	7/17 (42%)	7/17 (42%)

ICU = intensive care unit. CNS = central nervous system.

primary localisation of the disease was within the CNS. Three-month survival of patients with a CNS localisation was not worse compared with patients with extracranial lymphomas.

Discussion

Our study describes the characteristics and outcomes of 68 patients with a history of haematological malignancy being admitted to the ICU for a neurological event.

Seizures were the leading reason for ICU admission in our study. At 29%, this was substantially more than the 6% reported in a large neurocritical care study, regardless of the underlying disease.[8] This may be partly explained by a high incidence of epileptic seizures in patients after haematopoietic stem cell transplantation, caused by drug toxicity, CNS infection, metabolic encephalopathy or white matter lesions.[14] Outcomes were relatively good in patients admitted for seizures. ICH was the second leading reason for admission. The median platelet count on admission was not found to be significantly lower in these patients than in other patient groups, so did not explain the ICH. However, a study comparing prophylactic and therapeutic platelet transfusion in patients with haematological malignancy suggests that patients with AML benefit from prophylactic platelet transfusion when their platelet count is $< 10 \times 10^9$/L because of the higher risk of fatal ICH.[15] However, as the incidence of ICH in patients with haematological malignancies is low, the role of prophylactic platelet transfusion remains a matter for debate.[16] In our study, patients admitted with ICH mostly had AML, so it may be postulated that the risk of ICH is somehow related to the type of haematological malignancy regardless of platelet count, but this statement would require further research. The ICU LOS was longest in patients with myopathy/neuropathy. This might be related to the longer duration of MV in this group of patients (median, 18 days; IQR, 5–46 days), although this parameter was not statistically different between the neurological conditions.

The diversity of haematological conditions in our cohort is comparable to a recent study in ICU patients admitted with

Table 4. Characteristics of patients surviving at 3 months and non-survivors

Characteristic	Survivors ($n = 34$)	Non-survivors ($n = 34$)	*P*
Median age, years (IQR)	53 (41–62)	52 (42–62)	0.93
Male, *n* (%)	50	50	1.00
Median APACHE II score (IQR)	20 (14–26)	25 (20–30)	0.02
On mechanical ventilation < 24 hours after ICU admission, *n* (%)	44	56	0.15
Median time in hospital before ICU admission, days (IQR)	4 (0–21)	6 (0–25)	0.35
Median Glasgow coma score on admission (IQR)	13 (8–15)	10 (3–15)	0.17
Stem cell transplantation (autologous or allogeneic), *n* (%)	53	47	0.81
Active haematological disease, *n* (%)	47	53	0.80
Neutropenic, *n* (%)	40	60	0.34
Median platelet count on admission, 10^9/L (IQR)	113 (55–202)	39 (17–92)	< 0.01

IQR = interquartile range. APACHE = Acute Physiology and Chronic Health Evaluation. ICU = intensive care unit. GCS = Glasgow coma scale.

haematological disease, with NHL and AML being the main underlying haematological malignancies at ICU admission.[17] The hospital and 3-month mortality rates (39% and 48%, respectively) in this large prospective study, with over 1000 ICU patients with haematological malignancy, are comparable to our observed rates (37% and 50%, respectively). However, in a cohort of 1155 neurocritical care patients, regardless of the underlying disease, the observed ICU mortality was 10% lower than in our cohort.[8] Another large retrospective study in neurocritical care patients found a hospital mortality of 23%, which is also lower than what we observed.[18] We may therefore conclude that outcomes for our study patients were comparable to outcomes for ICU patients with a haematological malignancy as a whole, but were worse than for patients with a primary neurological event without a history of haematological malignancy necessitating ICU admission. The underlying haematological malignancy thus seems to have far more impact on outcome than the neurological event warranting ICU admission. Differences in severity of illness, treatment practice or treatment options might also account for the difference in mortality rates between our study population and the studies performed in neurocritical care patients.

Numerous factors have been found to be associated with mortality in patients with haematological malignancy who are admitted to the ICU. These include active haematological disease, time to ICU admission of more than 24 hours when a patient is already admitted to a hospital, allogeneic stem cell transplantation, requirement for MV, and need for vasoactive drugs.[17] In addition, neutropenia, the need for vasopressors, invasive MV and serum creatinine were found to be independent prognostic factors for in-hospital death.[19] In our population, non-survivors had lower platelet counts at admission and higher APACHE II scores than survivors, but other investigated factors were comparable between survivors and non-survivors.

Although the cohort we describe represents a small subgroup of patients with a haematological malignancy warranting ICU admission, we believe our results are unique because of the patient population and extensiveness of data collection. We believe that no patients were missed for inclusion because after screening of the Dutch NICE database, data were verified and completed through additional searches of local databases.

Our study has some limitations. First, results are limited by the retrospective study design. Second, introducing a selection bias on ICU admission might be an inevitable consequence of ICU admission policy. The median APACHE II score of our patient population was 23 (compared with a score of 21 of the total group of patients with a history of haematological malignancy admitted to the ICUs during the study period), so we do not believe that clinicians refused to admit our patients because of an expected high mortality risk. Nevertheless, selection bias in retrospective ICU cohort studies cannot be ruled out. Data on functional outcomes of patients would have been relevant but these data were not available for all patients. Our study might also seem to have included many patients who had received an allogeneic stem cell transplantation compared with autologous transplantation. This might be due to the higher rate of neurological complications after allogeneic transplantation, warranting ICU admission, or because the university hospitals collecting the study data overall perform more allogeneic than autologous transplantations, as is the current trend.[20] Lastly, evolving medical practices and treatments might influence baseline and outcome parameters of today's patients admitted to the ICU.

Conclusion

We show that neurocritically ill patients with a haematological malignancy have a similar prognosis compared with haematological patients without concomitant neurological events admitted to an ICU. Our findings emphasise that restrictions in ICU care are not justified for this patient population.

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Competing interests

None declared.

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