ORIGINAL ARTICLE

Port J Nephrol Hypert 2011; 25(2): 145-150
Advance Access publication 12 April 2011

Outcome of critically ill patients with haematological malignancies treated with renal replacement therapy

Paulo Santos[1], José Maximino[1], Ana Paiva[1], António J. Baldaia[1], Alfredo Loureiro[1], Filomena Faria[2]

[1]Nephrology Department and [2]Intensive Care Unit
Portuguese Institute of Oncology. Oporto, Portugal.

Received for publication: 09/02/2011
Accepted in revised form: 05/04/2011

ABSTRACT

Background: In the last few decades, survival of patients with haematological malignancies has substantially improved. However, those patients who develop life-threatening complications such as acute kidney failure still have an unfavourable prognosis. We aimed to characterise prognostic factors and outcome of onco-haematological patients in intensive care units with acute kidney injury treated with renal replacement therapy.

Methods: We performed a single-centre retrospective observational study.

Results: Between 1 January 2000 and 31 August 2009 62 onco-haematological patients treated in intensive care unit underwent continuous renal replacement therapy and/or slow efficiency haemodialysis. There was a male predominance (63%), and mean age was 46.4±17 years. The main reasons for admission were respiratory failure (94%) and septic shock (69%). Mean APACHE II and SAPS II scores at admission were 28±7.4 and 63±18.8, respectively. 50% presented with neutropoenia and 44% were bone marrow transplanted. 84% were on invasive ventilation. The median time on renal replacement therapy was 7 days and median intensive care stay was 10 days. Intensive care unit, hospital and 6-month mortality were, respectively, 66%, 86 % and 92%. In univariate analysis, variables correlated with mortality were invasive ventilation (in-intensive care unit death: 75% *vs.* 20%, $p<0.05$) and previous bone marrow transplant (in-intensive care unit death: 82% *vs.* 54%, $p<0.05$). Severity scores at admission, type of haematological malignancy and neutropoenia were not correlated with mortality. In multivariate logistic regression analysis, only two variables were independently associated with outcome: invasive ventilation (OR 17.9; 95% CI 1.7-184) and male gender (OR 4.6; 95% CI 1.1-19.4).

Conclusions: Critically ill onco-haematological patients treated with continuous renal replacement therapy have high intensive care unit mortality rate. However, it is comparable to that described in literature for non-oncological patients who perform continuous renal replacement therapy in general intensive care unit, despite higher hospital mortality. Need for invasive ventilation and male gender correlate with a worse outcome.

Key-Words:
Haematological malignancies; renal replacement therapy.

INTRODUCTION

Over the last few decades, survival of patients with haematological malignancies has substantially improved as a result of better supportive therapy, new and intensive chemotherapeutic agents and bone marrow transplant[1]. However, life-threatening complications such as acute kidney injury (AKI) have become more frequent, and the evaluation of risks and benefits of their treatments may be difficult and unclear[1,2].

Acute kidney injury is a frequent condition in hospitalised cancer patients[3]. Its incidence is 12-49% in haematologic patients admitted to intensive care units (ICU), and renal replacement therapy (RRT) is needed in 9-32%[2,4]. The high incidence of acute renal failure in these patients results from several factors such as higher susceptibility for sepsis, contrast induced nephropathy, acute tumour lysis syndrome, a more pronounced severity of illness, use of nephrotoxic drugs and specific bone marrow transplantation-related syndromes such as veno-occlusive disease or haemolytic uraemic syndrome[3,4].

In-ICU mortality and acute hospital mortality of patients with haematological malignancies remain high, close to 43.1% and 59.2%, respectively[11]. Patients who need RRT have a worse outcome, with ICU mortality reaching 80%[3]. The available studies on AKI in ICU onco-haematology patients focus mainly on bone marrow transplant recipients, and in this group mortality may rise to more than 85%[3,13]. In this study we aimed to characterise prognostic factors and outcome of onco-haematological patients in ICU with AKI and need for renal replacement therapy.

PATIENTS AND METHODS

Oporto`s Portuguese Institute of Oncology is a cancer hospital with 307 beds. It has an ICU with 8 beds and admits both medical and surgical patients.

We performed a single-centre retrospective observational study of the patients admitted to the ICU between 1 January 2000 and 31 August 2009 who met the criteria of underlying haematological malignancy and AKI on admission or during ICU stay requiring continuous RRT (haemofiltration and haemodiafiltration) and/or slow efficiency haemodialysis (SLED). Recipients of bone marrow transplant were included in the study. Oporto`s Portuguese Institute of Oncology Ethics Committee approval of the study was obtained.

The following variables were retrospectively collected from computerised databases and patients' records: age, sex, type of haematological malignancy, bone marrow transplantation, primary reason for ICU admission, presence of neutropoenia (neutrophil count ‹500/mm^3), calculated severity scores Acute Physiology and Chronic Health Evaluation II (APACHE II) and Simplified Acute Physiology Score II (SAPS II) within the first 24 hours of ICU admission, mode and duration of performed ventilation (noninvasive and invasive mechanical ventilation), RRT (time to RRT and duration) and length of stay. ICU, hospital and 6-month mortality and follow-up were also noted.

Septic shock was defined using the criteria of the American College of Chest Physicians/Society of Critical Care Medicine consensus conference. Acute kidney injury was defined according to RIFLE criteria (I or higher). Continuous variables were expressed as median. Categorical variables were compared by Chi-square or Fisher`s exact test. The influence of variables on ICU mortality was studied by multivariate logistic regression model. A p‹0.05 was considered as statistically significant. All statistical tests performed used SPSS statistical software (SPSS, Chicago, IL).

Decisions regarding the indication for RRT and the initial RRT modality are made in agreement with nephrology consultants. Both continuous and intermittent modalities are available in the ICU. We selected only patients who underwent continuous and/or hybrid therapy – venovenous haemofiltration, venovenous haemodiafiltration and slow efficiency haemodialysis (SLED).

RESULTS

Patient Population

During the study period 62 patients with haematological malignancy required RRT for AKI. Of these, 39 (63%) were men and 23 (37%) women (Table I). The mean age was 46.4±17 (8-80) years. There were 8 paediatric patients and 9 patients older than 65 years.

The main reasons for admission were respiratory failure in 54 patients (94%) and septic shock in 43 patients (69%). Mean APACHE II and SAPS II scores at admission were 28±7.4 and 63±18.8, respectively. Fifty-two (84%) had acute kidney injury at admission (Table I).

All patients were ventilated. Ten patients (16%) needed only noninvasive ventilation (NIV) and 52 patients (84%) invasive ventilation (IV). Sixteen patients (26%) underwent both types of ventilation. Mean duration of invasive ventilation was 10±11 days.

The median time from ICU admission to RRT was 2 days. The median time on RRT was 7 days.

Outcome

The median ICU length of stay was 10 (1-58) days. Forty-one patients died in the ICU (66%). The overall in-hospital mortality was 86 % (53 deaths).

Of the 9 patients who survived to hospital discharge, 4 patients died during the 6-month follow-up period, which constitutes an overall 6-month mortality of 92%.

Prognostic Indicators of Outcome

Survivors had no significant different severity scores (APACHE II 25.6±6; SAPS II 58.3±16) when compared with nonsurvivors (APACHE II 28.9±8; SAPS II 64.6±20; p=NS for both) (Table II). There was no difference in age, ICU stay, duration of invasive ventilation, time until RRT start or RRT duration between the two groups.

In a univariate analysis the following variables were associated with ICU mortality (Table III): invasive ventilation (ICU death: 75 *vs.* 20%, $p<0.05$) and previous bone marrow transplant (in-ICU death: 82 *vs.* 54%, $p<0.05$). Male patients had higher mortality but without statistical significance (ICU death:

Table I

Patients' characteristics at admission (n= 62)

	N	Percentage
Demographics		
Age, year, mean	46.4±17 (8-80)	
Gender, male	23	37
Severity of illness		
APACHE II score	28 ± 7.4	
SAPS II score	63 ± 18.8	
Characteristics on ICU admission		
Respiratory failure	54	94
Septic shock	43	69
Acute kidney injury	52	84
Neutropoenia	31	50
Type of haematologic malignancy		27
Acute myelogenous leukaemia	17	24
Acute lymphoblastic leukaemia	15	19
Non-Hodgkin's lymphoma	12	10
Myelodysplasic syndrome	6	10
Multiple myeloma	6	5
Chronic lymphocytic leukaemia	3	2
Hodgkin's disease	1	2
Chronic myelogenous leukaemia	1	2
POEMS syndrome	1	
Previous BMT	27	44

APACHE (Acute Physiology and Chronic Health Evaluation)
SAPS (Simplified Acute Physiology Scale); BMT (bone marrow transplantation)
ICU (Intensive Care Unit)
POEMS (Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes)
BMT (bone marrow transplantation)

Table II

Comparison between UCI survivors and non-survivors

	Alive	Dead	p
Age (yrs)	46 ± 21	46 ± 15	0.06
APACHE II score	25.6 ± 6	28.9 ± 8	0.21
SAPS II score	58.3 ± 16	64.6 ± 20	0.09
Time from ICU admission to RRT (days)	2.9	3.9	0.29
RRT duration (days)	13	10	0.57
IV duration (hours)	284.8	263	0.89
ICU stay (days)	15.8	13.5	0.43

RRT (renal replacement therapy); IV (invasive ventilation); ICU (Intensive Care Unit);

Table III

In-ICU mortality per subgroups

	N (%) of Deaths Per Total in Subgroups	P
Gender		
Male	29 (74.4)	0.09
Female	12 (52)	
Acute leukaemia		
Yes	17 (53)	
No	23 (77)	0.18
Non-Hodgkin's lymphoma		
Yes	10 (83)	
No	30 (61)	0.19
Multiple myeloma		
Yes	3 (60)	
No	3 (60)	0.9
Chronic leukaemia		
Yes	2 (67)	
No	5 (50)	0.9
Neutropoenia		
Yes	22 (71)	
No	19 (61)	0.59
Non-invasive ventilation		
Yes	19 (73)	
No	22 (61)	0.42
Invasive ventilation		
Yes	39 (75)	0.002
No	2 (20)	
Previous BMT		
Yes	22 (82)	0.032
No	19 (54)	

ICU (Intensive Care Unit); BMT (bone marrow transplantation)

Table IV

Multivariate analysis of prognostic factors for ICU mortality and survival

	OR (95% CI)	p
Male Gender	4.6 (1.1-19.4)	0.037
BMT	4.1 (0.94-17.7)	0.059
Invasive ventilation	17.9 (1.7-184)	0.015
APACHE II score	1 (0.8-1.17)	0.72
SAPS II score	1 (0.9-1)	0.86

BMT (bone marrow transplantation)
OR (odds ratio)
CI (confidence interval)
APACHE (Acute Physiology and Chronic Health Evaluation)
SAPS (Simplified Acute Physiology Scale)

74.4 *vs.* 52%, p=0.098). Type of haematological malignancy and neutropoenia were not associated with mortality (Table III).

The results of the multivariate logistic regression analysis are listed in Table IV. Only two variables were independently associated with outcome: invasive ventilation (OR, 17.9; 95% CI, 1.7-184) and gender (OR, 4.6; 95% CI, 1.1-19.4). There was a trend to higher mortality in bone marrow transplant patients (OR, 4.1; 95% CI, 0.94-17.7, p=0.059). Mean survival time of bone marrow transplant patients was 1.3±0.8 months. Mean survival time of non-bone marrow transplant patients was higher but not statistically significant different (5.8±3 months, p=0.438).

DISCUSSION

In our retrospective study of 62 patients with haematologic malignancy admitted to ICU who needed RRT for AKI, ICU and in-hospital mortality rates were 66% and 86%, respectively. This ICU mortality is similar to previous published series[5]. A more recent study reported higher in-ICU mortality and comparable in-hospital mortality[3]. Patients in this series had a similar male preponderance (63%), comparable incidence of invasive ventilation (median

incidence 87.8%), invasive ventilation duration (median 10 days) but were older (median age 62 years) and had higher APACHE II score (median 30). Darmon *et al.*[4] analysed outcomes in non-allotransplanted cancer patients, the majority with haematological malignancies (91.5%), admitted to ICU who required RRT and reported a lower in-ICU and in-hospital mortality (43.6 and 51.1%, respectively). However, in this study patients presented lower SAPS II score on ICU admission (SAPS score 53), less ventilatory support (63.8%) and allogenic bone marrow transplantation patients were excluded, probably contributing to the better reported survival rates.

Our results for ICU mortality approaches the overall ICU mortality rates reported in general ICU (non-oncological patients who need RRT) in which mortality is as high as 60%, as is the case of patients with septic shock[6]. However, 6 months' mortality is not comparable, with our patients presenting a low survival rate (8%).

The only factors present on admission that were associated with ICU-mortality were invasive ventilation and male gender. There was a trend to higher mortality in bone marrow transplant patients, although not reaching statistical significance.

In our study, both SAPS II and APACHE II failed to predict ICU mortality. A valuable scoring system could be a useful tool to facilitate intensive care treatment in this particular group of patients. Both SAPS II and APACHE II scores have been developed for general ICU and assessed in only small studies of critically ill haematological malignancy patients[7]. In some previous studies, these scores underestimated mortality or had no prognostic value in critically ill cancer patients[7-9]. Other studies report correlation with ICU mortality and in-hospital mortality[10-13], and that their value estimating outcome in a group of critically ill cancer patients but, at the same time, failing to predict individual outcome[7,14,15]. Hampshire *et al.*[16] found that both models showed reasonably good discrimination between survivors and nonsurvivors, but SAPS II score considerably underestimated hospital mortality and none showed good calibration.

In our analysis, neutropoenia, age and type of haematological malignancy were not significantly associated with outcome. Other studies report the same finding and support growing evidence that classic outcome predictors have no impact on survival[1,4,5,17,18].

The main prognostic factor was the use of invasive ventilation. Several previous studies described decreased survival with invasive ventilation use in haematological and solid cancer patients[1,19-22]. Hilbert *et al.*[20] found that early initiation of noninvasive ventilation in selected immunosuppressed patients (the majority as result of haematologic cancers and neutropoenia) with acute respiratory failure was associated with significant reductions in the rates of endotracheal intubation and serious complications and improved likelihood of survival ICU and hospital discharge. Ferrà *et al.*[21] analysed ICU mortality and prognostic factors for 100 critically ill patients with a haematologic malignancy admitted to ICU and found that the main predictors of a poor survival prognosis were mechanical ventilation (odds ratio 4.27; 95% CI 1.70-10.74; p=0.002) and haemodynamic instability. However, this is an unresolved issue. In fact, a recent retrospective study found that intensive care and in-hospital mortality of haematology patients with respiratory failure was not determinate by the type of initial respiratory support, raising the question that the expected beneficial effect of noninvasive ventilation may be overestimated[23].

Bone marrow transplant patients have a poor outcome when admitted to the ICU, despite reported improvements over recent years[24,25,26]. When respiratory failure occurs and mechanical ventilation is required, dramatic reduction in survival occurs[26,27]. Acute kidney injury is associated with significantly higher mortality rates[28,29] and when it coexists with other organ failures, described mortality exceeds 80%[30]. This tendency appears in our results in univariate analysis, but BMT patients had no significant lower mean survival, and BMT was not a predictive factor in multivariate analysis.

In summary, this study shows that continuous renal replacement therapy is feasible in critically ill haematology patients, and that these patients have a better than expected ICU survival. Need for invasive ventilation is the most important prognostic factor.

Our study has some limitations. Because it was conducted in a single centre, possible selection

biases concerning differences in patterns of care (ICU admission/discharge policies, criteria for noninvasive and invasive ventilation and RRT therapy) cannot be ruled out. In addition, given the retrospective design, some data may be missing. Therefore our prognostic indicators need to be validated in a further prospective multicenter study.

Conflict of interest statement. None declared.

References

1. Cherif H, Martling CR, Hansen J, Kalin M, Björkholm M. Predictors of short and long term outcome in patients with hematological disorders admitted to the intensive care unit for a life-threatening complication. Support Care Cancer 2007;15:1393-1398
2. Soares M, Salluh J, Carvalho MS, Darmon M, Rocco JR, Spector N. Prognosis of critically ill patients with cancer and acute renal dysfunction. J Clin Oncol 2006;24:4003-4010
3. Benoit DD, Hoste EA, Depuydt PO, *et al.* Outcome in critically ill medical patients treated with renal replacement theraphy for acute renal failure: comparison between patients with and without haematological malignancies. Nephrol Dial Transplant 2005;20:552-558
4. Darmon M, Thiery G, Ciroldi M, Porcher R, Schlemmer B, Azoulay E. Should dialysis be offered to cancer patients with acute kidney injury? Intensive Care Med 2007;33:765-772
5. Lanore JJ, Brunet F, Pochard F, *et al.* Hemodialysis for acute renal failure in patients with hematological malignancies. Critical Care Medicine 1991;19:346-351
6. Uchino S, Kellum JA, Bellomo R, *et al.* Acute renal failure in critically ill patients: a multinational, multicenter study. J Am Med Assoc 2005;294:813-818
7. Den Boer S, F de Keizer N, De Jonge E. Performance of prognostic models in critically ill cancer patients – a review. Crit Care 2005;9:458-463
8. Massion P, Dive A, Doyen C, *et al.*Prognosis of hematologic malignancies does not predict intensive care unit mortality. Crit Care Med 2002;30:2260-2270
9. Silfvast T, Pettilä V, Ihalainen A, Elonen E. Multiple organ failure and outcome of critically ill patients with haematological malignancy. Acta Anaesthsiol Scand 2003;47:301-306
10. Lamia B, Hellot MF, Girault C, *et al.* Changes in severity and organ failure scores as prognostic factors in onco-hematological malignancy patients admitted to the ICU. Intensive Care Med 2006;32:1560-1568
11. Schellongowski P, Benesch M, Lang T, *et al.* Comparison of three severity scores for critically ill cancer patients. Intensive Care Med 2004;30:430-436
12. Cornet AD, Issa AI, van de Loosdrecht AA, Ossenkoppele GJ, Strack van Schijndel RJ, Groeneveld AB. Sequential organ failure predicts mortality of patients with haematological malignancy needing intensive care. Eur J Haematol 2005;74:51-516
13. Afessa B, Tefferi A, Dunn WF, Litzow MR, Peters SG. Intensive care unit support and Acute Physiology and Chronic Health Evaluation III performance in haematopoietic stem cell transplant recipients. Crit Care Med 2003;31:1715-1721
14. Benoit DD, Vandewoude KH, Decruyenaere JM, Hoste EA, Colardyn FA. Outcome and early prognotic indicators in patients with a hematologic malignancy admitted to the intensive care unit for a life-threatening complication. Crit Care Med 2003;31:104-112
15. Soares M, Fontes F, Dantas J, *et al.* Performance of six severity-of-illness scores in cancer patients requiring admission to the intensive care unit: a prospective observational study. Criti Care 2004;8:R194-R203
16. Hampshire AP, Welch CA, McCrossan LA, Francis K, Harrison DA. Admission factors associated with hospital mortality in patients with haematological malignancy admitted to UK adult, general critical units: a secondary analysis of the ICNARC Case Mix Programe Database. Critical Care 2009;13:R137
17. Azoulay E, Recher C, Alberti C, *et al.* Changing use of intensive care for haematological patients: the example of multiple myeloma. Intensive Care Med 1999;25:1395-1401
18. Soares M, Salluh JI, Ferreira CG, Luiz RR, Spector N, Rocco JR. Impact of two different comorbidity measures on the 6-month mortality of critically ill cancer patients. Intensive Care Med 2005;31:408-415
19. Azoulay E, Alberti C, Bornstain C, *et al.* Improved survival in cancer patients requiring mechanical ventilatory support: impact of noninvasive mechanical ventilatory support. Crit Care Med 2001;29;3:519-525
20. Hilbert G, Gruson D, Vargas F, Valentino R, Gbikpi-Benissan G, Dupon M. Noninvasive ventilation in immunosupressed patients with pulmonary infiltratres, fever, and acute respiratory failure. N Eng J Med 2001;344:481-487
21. Ferrà C, Marcos P, Misis M, Morgades M, Bordejé ML, Oriol A. Outcome and prognostic factors in patients with hematologic malignancies admitted to the intensive care unit: a single-center experience. Int J Hematol 2007;85:195-202
22. Merz T, Schär P, Bühlmann M, Takala J, Rothen H. Resource use and outcome in critically ill patients with hematological malignancy: a retrospective cohort study. Crit Care 2008;12:R75
23. Depuyt P, Benoit D, Roosens C, Offner F, Noens L, Decruyenaere J. The impact of the initial ventilatory strategy on survival in haematological patients with acute hypoxemic respiratory failure. J Critical Care 2010;25:30-36
24. Huarinaga AJ, Leyva FJ, Giralt SA, *et al.* Outcome of bone marrow transplantation patients requiring mechanical ventilation. Crit Care Med 2000;28:1014-1017
25. Shorr AF, Moores LK, Edenfield WJ, Christie RJ, Fitzpatrick TM. Mechanical ventilation in hematopoietic stem cell transplantation. Chest 1999;116:1012-1018
26. Pène F, Aubron C, Azoulay E, *et al.* Outcome of critically ill allogenic hematopoietic stem-cell transplantation recipients: a reappraisal of indications for organ failure supports. J Clin Oncol 2006;24:643-649
27. Rubenfeld GD, Crawford SW. Withdrawing life support from mechanically ventilated recipients of bone marrow transplants: a case for evidence-based guidelines. Ann Intern Med 1996;125:625-633
28. Kersting S, Koomans HA, Hené RJ, Verdonck LF. Acute renal failure after allogenic myeloablative stem cell transplantation: retrospective analysis of incidence, risk factors and survival. Bone Marrow Transplantat 2007;39:359-365
29. Parikh CR, McSeenney P, Schrier RW: Acute renal failure independently predicts mortality after myeloablative allogenic hematopoietic cell transplant. Kidney Int 2005;67:1999-2005
30. Parikh CR, Sandmaier BM, Storb RF, *et al.* Acute renal failure after nonmyeloablative hematopoietic cell transplantation. J Am Soc Nephrol 2004;15:1868-1876

Correspondence to:
Dr Paulo Santos
Nephrology Department
Portuguese Institute of Oncology
Av. António Bernardino de Almeida
4200-072 Oporto, Portugal
paulo.ads@gmail.com