Risk factors associated with pediatric intensive care unit admission and mortality after pediatric stem cell transplant: possible role of renal involvement

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Original article

Background: **Hematopoietic stem-cell transplant (HSCT) is associated with many risk factors for life-threatening complications. Post-transplant critical illness often requires admission to the pediatric intensive care unit (PICU).**

Methods: **A retrospective analysis was made on the risk factors associated with PICU admission and mortality of all HSCT patients at Helen DeVos Children's Hospital from October 1998 to November 2008.**

Results: **One hundred and twenty-four patients underwent HSCT, with 19 (15.3%) requiring 29 PICU admissions. Fifty patients received autologous, 38 matched sibling, and 36 matched un-related donor HSCT, with 10%, 13% and 25% of these patients requiring PICU admission, respectively (*P*=0.01). Among the HSCT patients, those who were admitted to the PICU were more likely to have renal involvement by either malignancy requiring nephrectomy or a post transplant complication increasing the likelihood of decreased renal function (21.1% *vs.* 4.8%, *P*=0.03). PICU admissions were also more likely to receive pre-transplant total body irradiation (52.6% *vs.* 27.6%, *P*=0.03). Among 29 patients with PICU admission, 3 died on day 1 after admission, and 5 within 30 days (a mortality rate of 17%). Thirty days after PICU admission, non-survivors had a higher incidence of respiratory failure and septic shock on admission compared with survivors (80% *vs.* 16.7%, *P*=0.01 and 80% *vs.* 4.2%, respectively, *P*=0.001). Two survivors with chronic renal failure underwent renal transplantation successfully.**

Conclusions: **Total body irradiation and renal involvement are associated with higher risk for PICU admissions after HSCT in pediatric patients, while septic shock upon admission and post-admission respiratory failure are associated with mortality.**

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Key words: **hematopoietic stem-cell transplant; intensive care; renal complications**

Introduction

Hematopoietic stem cell transplant (HSCT) is currently the treatment of choice for many malignant and some non-malignant conditions.[1-3] Advances in supportive care have resulted in improved acute phase therapy and long-term survival. However, a significant proportion of patients still die either from treatment toxicity or primary disease.[4-6] Transplant related toxicity includes immunosuppression with vulnerability to infection and end organ failure. In addition, patients suffer from the sequelae of pre-transplant organ damage caused by prior therapy, morbidity due to the underlying disease, conditioning regimen toxicity, higher risk of several infections at different phases post transplant, and graft versus host disease (GVHD) in the allogeneic setting.[6,7] Therefore, transplant patients often require admission to the pediatric intensive care unit (PICU).

Mortality rates continue to improve in this vulnerable patient population with adoption of early PICU admission protocols, improvement in patient/donor matching, conditioning therapy and PICU supportive care.[8,9] Studies aimed at predicting patient survival from both the general pediatric population and

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the oncology population have resulted in the creation and adoption of assessment tools such as pediatric risk of mortality (PRISM) score, oncologic pediatric risk of mortality (O-PRISM) score, and pediatric multi-organ dysfunction (PMOD) score.[10,11] However, none of them have been validated in the HSCT patient population. The approach to the care of the critically ill HSCT patient has evolved into a multispecialty care model requiring an integrated approach with an understanding of the goals for continued care and whenever indicated, shifting to palliative care. This study underscores the need to develop predictors of mortality and morbidity in this high-risk patient population. Therefore, we reviewed the peri-transplant risk factors to examine their effects on the risk of PICU admission, complications and mortality.

Methods

A retrospective 10-year chart review was performed in all pediatric patients who underwent HSCT at Helen DeVos Children's Hospital from the start of the program in October 1998 to November 2008. Patient demographics, characteristics and details of therapy and outcome were reviewed from the pre-existing HSCT database. Those admitted to the PICU had their medical records reviewed to collect all pertinent information about medical complications, interventions, PICU acuity (PRISM, O-PRISM and PMOD) scores and outcomes. The primary end-points were PICU admission and mortality at 30 days after admission, and the secondary end-points were 180-day post-admission mortality, medical complications and interventions in the PICU.

Patients after HSCT were admitted to the PICU if they had cardiac dysfunction with hemodynamic instability requiring inotropic support, pulmonary dysfunction with decompensation requiring at least 0.4 FiO_2, renal dysfunction requiring renal replacement therapy regardless of etiology, or hepatic dysfunction with altered level of consciousness or seizures. These patients were included in this review while those admitted for the following causes were excluded: routine post-operative care, plasmapheresis, central venous catheter placement, or hematopoietic stem cell harvesting. Renal involvement was defined as neoplastic infiltration with or without nephrectomy and/or post-transplant complications such as thrombotic microangiopathy. In the present study, renal dysfunction was defined as a renal injury requiring renal replacement therapy because the patients required ICU care.

The Schwartz formula was used to estimate creatinine clearance:[12] creatinine clearance= (K×Ht)/serum creatinine (K=constant based on age/weight).

Descriptive statistics was used to describe the variables. The Mann-Whitney U test was used to compare numerical variables, the Chi-square test or Fisher's exact test was utilized to test the differences between qualitative variables, and odds ratios were used to describe the risk of mortality.

Results

One hundred and twenty-four patients underwent HSCT, with 19 patients (15.3%) requiring 29 PICU admissions. Fifty patients received autologous, 38 matched sibling donor, and 36 matched unrelated donor HSCT, with 10%, 13%, and 25% of the 3 groups requiring PICU admissions respectively (P=0.01). The patients admitted to the PICU had a significantly higher incidence of renal involvement (21.1% *vs.* 4.8%, P=0.03), and most of them had received total body irradiation before HSCT (52.6% *vs.* 27.6%, P= 0.03).

HSCT patients who required ICU admissions were older and heavier. Furthermore, patients who received peripheral blood stem cells compared to other sources had fewer admissions to the PICU (16% *vs.* 84%, P=0.05) because this source was almost exclusively used in the autologous type of transplant at our center, which is inherently associated with a less complicated post-transplant course. There were no differences between these groups. However, with regards to other

Table 1. Patient demographics and pediatric intensive care unit (PICU) admissions

Demographics	No PICU admission n=105	PICU admission n=19	P value
Age (y)	8.2 ± 5.9	11.2 ± 6.3	0.07*
Height (cm)	122.0 ± 36.0	145.0 ± 37.0	0.04*
Weight (kg)	+ 33.9 ± 25.8	47.0 ± 32.1	0.03‡
Females, n	60 (57.1%)	10 (52.6%)	0.7‡
Primary diagnosis			
Leukemia/lymphoma	48 (45.7%)	12 (63.2%)	0.3‡
Solid tumors	33 (31.4%)	4 (21.1%)	
Others	23 (21.9%)	3 (15.8%)	
Graft sources			
Peripheral blood	41 (39.0%)	3 (15.8%)	
Cord blood or bone marrow	64 (61.0%)	16 (84.2%)	0.05‡
Renal involvement	5 (4.8%)	4 (21.1%)	0.03†
CMV (+) donor or recipient	16 (15.2%)	6 (31.6%)	0.1†
Total body irradiation	29 (27.6%)	10 (52.6%)	0.03‡
Types of HSCT			
Autologous	45 (42.9%)	5 (26.3%)	
Allogeneic sibling	33 (31.4%)	5 (26.3%)	0.1‡
MUD	27 (25.7%)	9 (47.4%)	

*: Mann-Whitney U test; †: Fisher's exact test; ‡: Chi-square test; MUD: matched unrelated donor; CMV: cytomegalovirus; HSCT: hematopoietic stem-cell transplant.

variables (Table 1) during the 29 PICU admissions, 3 patients died on day 1 after admission, 5 within 30 days (a mortality rate of 17%), and 7 within 180 days (a mortality rate of 24%) (Table 2).

In the 10-year study period, there was no significant change in PRISM scores on the first admission to the PICU; furthermore, the mortality at 30 days or 180 days was not varied in the first 5 years compared to the second 5 years. Compared with survivors, non-survivors at 30 and 180 days after admission had similar PMOD scores and slightly higher O-PRISM scores on admission to the PICU (Table 3).

There were 5 deaths at 30 days when compared to 24 survivors; the nonsurvivors had a higher incidence of septic shock on admission to the PICU (80% *vs.* 16.7%, *P*=0.01) and a higher incidence of respiratory failure after admission (80% *vs.* 4.2%, *P*=0.001). All the deaths were due to failure of organs although one was also associated with relapse. There was a tendency for post-admission cardiac dysfunction (40% *vs.* 4.2%, *P*=0.06), renal failure (40% *vs.* 12.5%, *P*=0.1), and more frequent PICU interventions. The interventions

Table 2. Non-survivors at 180 days after pediatric intensive care unit (PICU) admission

Age at BMT (y)	Weight (kg)	Diag. prior to SCT	Time from HSCT to PICU (mon)	Time of death from HSCT (mon)	Time of death from PICU admission (mon)	Malignant renal involvement	TBI	Need for mechanical ventilation	Need for CRRT	Cause of death	Diagnosis on PICU admission	PICU complications
3.5	16.5	LL	47	53	6	N	N	Y	N	Recurrent disease	Post-mass resection	None
16.2	110.8	LL	5	6	1	N	N	N	N	MOSF	Sepsis, respiratory distress, encephalopathy	Respiratory failure, disseminated aspergillosis
9.5	29.8	ST	6	6	0	N	N	N	N	Recurrent disease/MOSF	V-P shunt malfunction	None
16.7	116.0	LL	2	3	1	N	Y	Y	Y	MOSF	Sepsis, respiratory distress	Respiratory failure, renal failure
21.0	79.8	LL	1	3	2	N	Y	N	Y	Recurrent disease	Renal failure	Coagulopathy bacteremia, MOSF
17.8	65.5	LL	26	27	1	Y	Y	Y	Y	Cardiac failure	Sepsis, hypotension	MOSF
1.3	6.8	LL	3	3	0	N	N	Y	N	ARDS	Hypotension, respiratory distress	Respiratory failure, heart failure

LL: lymphoma leukemia; ST: solid tumors; O: others; Y: yes; N: no; MOSF: multi-organ system failure; ARDS: acute respiratory distress syndrome; BMT: bone marrow transplant; SCT: stem cell transplant; HSCT: hematopoietic stem cell transplant; TBI: traumatic brain injury; CRRT: continuous renal replacement therapy.

Table 3. Characteristics of patients at 30 days after pediatric intensive care unit (PICU) admission

		Survival at 30 days (*n*=24)	Non-survival at 30 days (*n*=5)	*P* value
	Time from BMT to PICU admission (d)	403.0 ± 434.0	252.0 ± 305.0	0.5*
	Pre BMT creatinine clearance	93.0 ± 51.0	108.0 ± 82.0	0.8*
	Total body irradiation	15 (62.5%)	2 (40.0%)	0.6†
	PICU length of stay (d)	7.2 ± 10.0	12.0 ± 11.0	0.2*
	O-PRISM score	4.1 ± 5.4	9.4 ± 11.7	0.2*
	PMOD score	3.2 ± 2.8	3.2 ± 1.9	0.8*
Reason for PICU admission	Septic shock	4 (16.7%)	4 (80.0%)	0.01†
	Heart dysfunction	2 (8.3%)	0	
	Hypertension	3 (12.5%)	0	
	Pulmonary dysfunction	2 (8.3%)	3 (60.0%)	0.1†
	Renal dysfunction	6 (25.0%)	0	
	Hepatic dysfunction	2 (8.3%)	0	
PICU interventions	Mechanical ventilation	6 (25%)	3 (60.0%)	0.2†
	Inotropic support	1 (4.2%)	2 (40.0%)	0.06†
	Renal replacement	2 (8.3%)	3 (60.0%)	0.1†
PICU complications	Pulmonary dysfunction	1 (4.2%)	4 (80.0%)	0.001†
	Heart dysfunction	1 (4.2%)	2 (40.0%)	0.06†
	Renal dysfunction	3 (12.5%)	2 (40.0%)	0.1†
	Hepatic dysfunction	2 (8.3%)	0	
	Coma	1 (4.2%)	0	
	Coagulopathy	1 (4.2%)	0	
	Infection	5 (20.8%)	0	

*: Mann-Whitney *U* test; †: Fisher's exact test; PMOD: pediatric multi-organ dysfunction score; O-PRISM: oncologic pediatric risk of mortality score; BMT: bone marrow transplant.

included mechanical ventilation (60% *vs*. 25%, *P*=0.2), inotropic support (40% *vs*. 4.2%, *P*=0.06), and continuous renal replacement therapy (40% *vs*. 12.5%, *P*=0.1). There was no difference in age, gender, race, primary diagnosis, graft type or conditioning regimen (Table 3).

The mortality rate at 180 days after PICU admission was 37% (7/19 patients) or 24% (7/29 admissions). Three of the 7 patients died from primary malignant disease. Compared to PICU survivors (*n*=22), non survivors at 180 days post PICU admission (*n*=7) had a higher incidence of respiratory failure during PICU stay (57% *vs*. 4.5 %, *P*=0.007) and a trend towards higher incidence of sepsis (57% *vs*. 18%, *P*=0.06). On PICU admission, non-survivors compared to survivors required one or more PICU interventions such as mechanical ventilation, inotropic support and/or CRRT (5/10, 50% *vs*. 2/19, 10.5%, *P*=0.03). Patients who required one or more PICU interventions had a higher risk of mortality (OR=8.5, 95% CI: 1.25-57.93) (Table 2).

Nine patients in our cohort had renal involvement, and mortality was 44% (4/9) with 50% (2/4) in the PICU and 40% (2/5) not requiring PICU admission. HSCT patients with renal involvement were more likely to be admitted to PICU compared those without, (21.1% [4/19] *vs*. 4.8% [5/105], *P*=0.03) , Five patients showed renal involvement with pre-transplant nephrectomy secondary to Wilms tumor, neuroblastoma or post-transplant partial nephrectomy. Imaging studies showed infiltration of the kidneys caused by Hodgkin's disease in one patient. In the remaining 3 patients, renal involvement was related to BMT-related thrombotic microangiopathy or mesangial lysis syndrome. HSCT patients with renal involvement at PICU admission had a median glomerular filtration rate of 96.9 mL/min per 173 m^2, which decreased to 56.2 mL/min per 173 m^2 by the end of ICU stay. Two of these patients eventually underwent renal transplantation (Table 4).

Discussion

HSCT is curative for a number of malignant, hematological and metabolic diseases. However, 10%-25% of these patients require intensive care support. In our study, 19 (15.3 %) of the 124 patients were admitted to the PICU during the study. After PICU admission, the 30 day mortality was 26%. The 180 day mortality was 7 of 19 patients (37%). Three of these patients had recurrent disease and one of them suffered from multi-organ system failure (MOSF) as well.

Patients receiving autologous transplant had less risk of PICU admission and/or mortality, whereas those who received total body irradiation, likely reflecting allogeneic type of treatment, were at higher risk to require PICU admission. The other risk factors predicting higher mortality after PICU admission include septic shock and late development of respiratory failure. Traditional PICU scores such as PMOD and O-PRISM are not predictive of PICU outcomes.

Historically, the outcome of HSCT patients after admission to PICU has been improving, and the mortality rate has declined from 91% to 25% over the past three decades.[9,13,14] The 30-day mortality in our study, a reasonable analogue of outcome after admission to PICU, does reflect that trend. Similar to other studies, the 5 deaths (17%) of 29 PICU patients were due to organ failure, with one patient showing signs of relapse.[9] This improvement may be attributive to better supportive care in ICU and/or better patient/

Table 4. Patients with renal involvement

	Age/Sex	Transplant type	Primary disease	Time between renal involvement and HSCT(mon)	Time from HSCT to PICU (mon)	Outcome	Time to death from transplant (mon)	Biopsy results	Cr CL on PICU admission	Cr CL on PICU discharge
PICU patients	15 y/F	Allogeneic	Chronic myelogenic leukemia	7 mon after HSCT	8	Renal transplant	N/A	TMA after renal transplant	106.5	35.5
	15 y/F	Allogeneic	Acute myelogenic leukemia	12 mon after HSCT	12	Renal transplant	N/A	Clinical TMA	87.2	50.8
	3 y/F	Autologous	Neuroblastoma	6 mon before HSCT	0.5	Expired	16	Surgical resection	61.6	61.6
	18 y/F	Allogeneic	Hodgkin disease	2 mon before HSCT	12	Expired	38	No biospy	178.2	267*
Non PICU patients	5 y/M	Autologous	Wilms tumor	24 mon before HSCT	_	Alive & well	N/A	Wilms nephrectomy	N/A	N/A
	13 y/M	Allogeneic	T cell lymphoma	5 mon after HSCT	_	Mild renal dysfunction	N/A	Mesangial lysis syndrome	N/A	N/A
	4 y/F	Autologous	Neuroblastoma	19 mon after HSCT	_	Alive & well	N/A	Partial nephrectomy	N/A	N/A
	5 y/F	Autologous	Wilms tumor	14 mon before HSCT	_	Expired	4	Wilms nephrectomy	N/A	N/A
	9 y/M	Autologous	Wilms tumor	19 mon before HSCT	_	Expired	6	Wilms nephrectomy	N/A	N/A

TMA: thrombotic microangiopathy; F: female; M: male; N/A: not available; HSCT: hematopoietic stem-cell transplant; ALL: acute lymphocytic lymphoma; Cr CL: creatinine clearance (estimated); *: Patient's creatinine clearance level was obtained while the patient was on continuous renal replacement therapy; PICU: pediatric intensive care unit.

donor selection, especially to the introduction of high resolution human leukocyte antigen typing, which has significantly reduced the incidence and severity of GVHD.[8,15]

Our study showed that patients with renal involvement are more likely to be admitted to the PICU and have a higher mortality. Studies[16-20] have shown that acute kidney injury occurs for various reasons in HSCT patients, and that it is an independent risk factor for ICU admission. Once acute kidney injury occurs with need for dialysis, outcomes may be poor as reported in a study that only 1 of 29 patients requiring renal replacement therapy after HSCT survived more than 6 months.[18] Five of our patients had renal involvement before HSCT, including a nephrectomy or infiltration by Hodgkin's disease. HSCT patients often have increased risks for bleeding and infection, making a renal biopsy for an accurate pathological diagnosis risk. However, 3 patients had clinically or biopsy proved renal thrombotic microangiopathy or mesangial lysis syndrome after HSCT.

HSCT patients often have inadequate muscle mass to generate adequate serum creatinine, and currently most formulas estimate renal function utilizing serum creatinine level. Therefore, in these patients it may be more suitable to measure glomerular filtration rate and/or potentially to measure cystatin C prior to the administration of nephrotoxic agents.[21,22] Two of the allogeneic HSCT patients with renal disease did eventually undergo renal transplantation. One received a kidney from her bone marrow donor, and was no longer given immunosuppressive therapy. The other patient received a kidney from the bone marrow donors' brother but required immunosuppressants.

In conclusion, the present study is limited by its retrospective single center study design. However, this adds uniformity to the way for patient management and reflects findings in other similar programs. The results suggest that as outcomes continue to improve, PICU intervention and renal involvement still place HSCT patients at an increased risk. With the improvement of outcomes, options such as renal transplantion are considered for HSCT patients with end-stage renal disease and therefore require further study.

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