Continuous Kidney Replacement Therapy in Children with Sinusoidal Obstruction Syndrome After Hematopoietic Cell Transplant: Outcome and Liberation

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Abstract

Background: Sinusoidal obstruction syndrome (SOS), a serious complication after hematopoietic cell transplant (HCT), is associated with multi-organ dysfunction (MOD) and a high mortality rate. In severe cases, continuous kidney replacement therapy (CKRT) is initiated to manage fluid overload (FO) and acute kidney injury. Studies that evaluate the use of CKRT in this population are lacking. The aim of our study was to assess the outcome of critically ill children with severe SOS post HCT who received CKRT. We also sought to assess factors associated with survival and liberation post CKRT. **Procedure:** Retrospective review of all children admitted to the intensive care unit (ICU) with SOS post HCT who received CKRT from January 2010 to August 2022. **Results:** Among the 53 children who received CKRT post HCT, 13 had severe SOS. The median age was 6 years; 62% were males, and most (77%) received allogeneic HCT. In this cohort, 92% required respiratory support and 85% required vasopressor support. The ICU survival rate was 62%. Survivors experienced lower cumulative FO on the 2 days following CKRT initiation (-4.2% in survivors versus -0.5% in non-survivors, p=0.07). Higher urine output on D1 and D2 after discontinuation of CKRT was associated with successful liberation. **Conclusions:** In this study of post-HCT children with SOS and MOD who received CKRT, 62% survived until ICU discharge. This survival rate is encouraging as it approximates the survival rates of general pediatric cohorts treated with CKRT. Reducing FO after initiation of CKRT can improve survival in these children.

Introduction

Sinusoidal obstruction syndrome (SOS), formerly known as veno-occlusive disease (VOD), is a serious complication encountered in the early phase post hematopoietic cell transplant (HCT). The pathogenesis of SOS involves injury to the sinusoidal endothelial cells of the liver, resulting in increased vascular permeability and narrowing of the sinusoids, slowing the blood flow within the vascular lumen (1, 2). The incidence of SOS is typically 5% to 13% but is reported to be higher in the pediatric high-risk population (20-60%) (1-3). Severe SOS is associated with multi-organ dysfunction (MOD) and a higher rate of mortality. Acute kidney injury (AKI) seen in SOS is secondary to kidney hypoperfusion, vasoconstriction, portal hypertension, and fluid overload (3-5). In addition, intra-abdominal hypertension can exacerbate pre-existing kidney injury (3). SOS increases the risk of AKI by 6.02 times in these patients (4). Despite treatment advances, such as the introduction of defibrotide that contributed to reduced mortality and reversal of organ dysfunction, mortality continues to be high if MOD is present, with a 100-day estimated survival rate of only 28% in defibrotide-treated patients (adults and children) who had both ventilator and dialysis dependence (6).

Continuous kidney replacement therapy (CKRT) is used to manage severe AKI and to mitigate the effects of fluid overload (FO), both of which occur in children with SOS. Recent guidelines by the HCT subgroup of the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) and the Supportive Care Committee of Pediatric Blood and Marrow Transplant Consortium (PBMTC) recommended consideration of CKRT in children with SOS when FO is [?]10% (7). Studies that evaluate the use of CKRT in children with SOS following HCT are lacking. Therefore, we sought to examine the use of CKRT in a cohort of critically ill children with SOS following HCT. The primary objective of this study was to assess the outcome of critically ill children post-HCT with severe SOS who received CKRT therapy. In addition, our aim was to assess factors associated with survival and liberation post-CKRT.

Patients and Methods

Study Population

All children admitted to the intensive care unit (ICU) at St. Jude Children's Research Hospital, a specialized pediatric hematologic-oncology hospital, who received CKRT from January 2010 to August 2022 were screened. Patients were included if they underwent HCT and had SOS at the time of the CKRT course. The study was approved by the St. Jude Children's Research Hospital Institutional Review Board. The PrismaFlex CKRT system (Gambro/Baxter) was used for all patients. All patients received continuous regional citrate infusion for anticoagulation and continuous systemic calcium infusion.

Definitions

SOS diagnosis and grading were based on the European Society for Blood and Marrow Transplantation (EBMT) Pediatric Criteria (8). AKI was defined and staged according to Kidney Disease Improving Global Outcomes (KDIGO) guidelines (9). AKI was classified as severe if it was stage 2 or 3 per KDIGO classification. Fluid overload was calculated according to the formula described by Goldstein et al.: FO % = Fluid in - fluid out (L) / intensive care admission body weight in kg $\times$ 100 (10). Cumulative fluid overload is the sum of daily FO % before or after CKRT. For example, cumulative FO D-3 = (FO% D-3 + FO%D-2 + FO% D-1). All patients were challenged with diuretics if they did not have adequate urine output after stopping CKRT. Successful liberation was defined as patients who did not require CKRT or other dialysis modality for at least 72 h after discontinuation of CKRT.

Data collection

The following ICU course data were collected: patient demographics, primary oncologic diagnosis, type and number of transplants, Pediatric Risk of Mortality (PRISM) score, use of invasive mechanical ventilation (IMV) or positive pressure ventilation, vasopressor support, duration of IMV and CKRT course, ICU survival, and liberation from CKRT/further kidney replacement therapy (KRT). Daily fluid balance and urine output before, during, and after CKRT courses were recorded. In addition, daily laboratory data were recorded including basic metabolic profile, bilirubin, albumin, ammonia, liver function tests, prothrombin time, C-reactive protein (CRP), white blood count, and platelet count.

Statistical analysis

Descriptive statistics are presented as N (%) for categorical variables and median (Min, Max) for continuous variables. The Exact Wilcoxon rank-sum test was used to compare distributions of laboratory values by ICU survival and CKRT liberation. The exact chi-square test was used to compare categorical variables by ICU survival. P-values <0.05 are considered to be statistically significant. Median (Min, Max) are reported for all statistical tests. All analyses were conducted in SAS 9.4 (Carry, NC).

Results

Of the 53 children who were critically ill post HCT and received CKRT, 13 had severe SOS and were included in this study. The median age was 6 years, and 62% were males. Most (77%) had allogeneic HCT, with 54% being past their second transplant. All patients had severe SOS and were treated with defibrotide except one patient who had severe pulmonary hemorrhage. In our cohort, 10 patients were intubated and received

IMV; 2 received non-invasive positive pressure ventilation, and only one patient did not require positive pressure ventilation. Most required vasopressor support (85%), 9 (69%) were on vasopressor support before the initiation of CKRT. In our cohort, 69% received 3 organs support (IMV, vasopressors, and CKRT). Prior to CKRT initiation, AKI stage 3 was present in 77% of our cohort (Table 1). The timeline of the clinical course of all patients is depicted in Figure 1.

Survival

The overall ICU survival rate was 62%, with a 56% rate in the 9 children requiring both IMV and vasopressor support. The duration of the CKRT course and IMV treatment in survivors and non-survivors was similar (Table 1). Non-survivors had a significantly higher serum bilirubin level on D2 (4.7 mg/dL in survivors versus 11mg/dL in non-survivors, p=0.07) and on D3 following CKRT initiation (2.6 mg/dL in survivors vs 14.6 mg/dL in non-survivors, p=0.05) (Figure 2). Survival was not associated with serum levels of albumin, ammonia, prothrombin time, or CRP.

Prior to CKRT initiation, severe AKI was present in all survivors but only 40% of non-survivors (p=0.035). In addition, urine output was higher in non-survivors before CKRT initiation. On D-2 and D-1, respective median urine output was 0.4 and 0.4 ml/kg/h in survivors but 1.4 and 1.6 ml/kg/h in non-survivors (p=0.09 on D-1 and D-2.

Fluid overload

Cumulative FO D-3 through D-1 before CKRT initiation in our cohort was patients had cumulative FO<5% on the 2 days (FO D1, D2) following CKRT initiation. The median cumulative FO (D-1, D-2) before CKRT was 0.99% in survivors and 4.09 % in non-survivors. Survivors tended to experience lower cumulative FO on the 2 days (FO D1, D2) following CKRT initiation (-4.2% in survivors versus -0.5% in non-survivors, p=0.07) (Figure 3).

Liberation from CKRT

Of the 10 patients who survived their CKRT course, 5 had successful liberation from CKRT and did not require KRT within 72 h. Urine output was significantly higher in children who were liberated from CKRT than in those who were not (Figure 4). On D1 after discontinuation of CKRT, median urine output was 2.94 mL/kg/h in children with successful liberation and only 0.22 mL/kg/h in children who were not liberated (p=0.008). Similarly, median urine output was 3.46 mL/kg/h vs 0.11 ml/kg/h on D2 in children who were liberated versus not liberated respectively (p=0.016). However, urine output before CKRT initiation was not associated with successful liberation.

Discussion

The ICU survival rate in our cohort of critically ill children with severe SOS and MOD post HCT was 62%, despite most requiring respiratory and vasopressor support. Our mortality rate of 38% is lower than that reported in other recent post-HCT cohorts with severe SOS and MOD. In a large cohort of 71 critically ill adult patients with SOS post HCT who were treated with defibrotide, mechanical ventilation, vasopressors, and KRT were required in 59%, 52%, and 49% of patients, respectively (11). The overall ICU mortality rate was 54%; however, a higher mortality rate was observed in patients receiving IMV (84%), vasopressor support (79%), or KRT (71%), and among their 28 patients who required mechanical ventilation and renal replacement therapy, the hospital mortality rate was 93% (11). Another large cohort of 651 post-HCT patients (adults and pediatrics) pooled from 3 studies reported an estimated D100 survival rate of 38% in patients with both ventilator- and dialysis-dependence and 40% in patients with one dependence (12). Our ICU survival rate approximates the recently reported rate of 64% in a general pediatric cohort of 980 patients treated with CKRT (13).

FO is an independent risk factor for mortality in critically ill children and can prolong the course of IMV and AKI (14). In a metanalysis of 44 studies (7,505 children), each 1% increase in FO resulted in a 6% increase in odds of mortality (14). Similarly, FO adversely impacts the outcome of children post HCT. In a multicenter

retrospective study of 68 critically ill children with cancer post HSCT (23 patients) who were receiving CKRT, patients with FO >10% at CKRT initiation were 6.16 times more likely to die than were those with FO [?]10% (15). Unfortunately, FO is common in children post HCT, especially in those in whom SOS develops. Capillary leak, portal hypertension-like pathophysiology leading to ascites, and refractory thrombocytopenia with subsequent need for frequent transfusions are factors that contribute to the development of FO in these patients (7). Initial management of FO includes fluid restriction and diuresis; however, CKRT should be considered when FO approaches >10%. In our cohort, FO was relatively low before starting CKRT, with FO 5% in survivors and non-survivors prior to CKRT initiation. This may have contributed to the lower mortality rate that was observed in our cohort. Following CKRT initiation, survivors in our cohort achieved less cumulative FO in the first 2 days compared to non-survivors

Urine output and the degree of AKI at the time of CKRT initiation were not associated with survival in our cohort. In fact, survivors had worse AKI before initiation of CKRT. Based on these findings, these parameters should not be used for prognosis and outcome prediction in these patients.

In our cohort, urine output was significantly higher in children who were successfully liberated from CKRT starting on the first day after CKRT. This suggests that good urine output after CKRT can serve as predictor of successful CKRT liberation. In a large pediatric cohort of 622 patients on CKRT, 54% were successfully liberated (16). Successful liberation was associated with a higher urine output prior to CKRT initiation. In our cohort, mechanical ventilation and urine output before CKRT initiation were not associated with successful liberation.

The limitations of our study include its retrospective design, small population, and absence of a control group. However, our study describes the largest pediatric cohort of post-HCT patients with severe SOS who received CKRT. This study spanned 12 years and offers valuable insight into the clinical course and outcome of these children. Prospective multi-institutional studies are required to further elucidate factors that improve these patients' rates of survival and successful liberation from CKRT.

In summary, in this cohort of children with SOS and MOD post HCT, the ICU survival rate was 62%. Survival was higher in children who experienced less FO on the 2 days following CKRT initiation. Successful liberation from CKRT was associated with higher urine output on the 2 days following the end of the course of CKRT. Our findings suggest that CKRT has the potential to improve ICU survival for post-HCT patients with severe SOS and MOD.

6 Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

7 Author Contributions

LE contributed to planning, writing, data collection, and editing the manuscript; MH contributed to data collection, writing, and editing the manuscript; CC and EA contributed to data analysis and manuscript writing; and RE contributed to planning and editing the manuscript. All authors approved the submitted version.

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Figure 1. Timeline of clinical course of children with SOS post HCT, * denotes non-survivors

Figure 2 . Laboratory values and survival

Figure 3 . FO and survival

Figure 4. Urine output and successful liberation from CKRT. D-1 represents the day before CKRT initiation and D+1 represents the day after CKRT discontinuation

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Table 1. Characteristics of survivors and non-survivors

Characteristic	**Survivors (8)**	**Non-Survivors (5)**	**P-value**
Age (y)	8.55(0.86,18.1)	3.23(1.02,19.0)	0.8329
Race			

Characteristic	Survivors (8)	Non-Survivors (5)	P-value
Black	1(12.5)	0	1
White	7(87.5)	5(100)	
Sex			
Male	4(50)	4(80)	0.5649
Female	4(50)	1(20)	
Primary diagnosis			
B-cell ALL	1(12.5)	3(60)	0.223
T-cell ALL	1(12.5	0(0)	
AML	4(50)	1(20)	
Lymphoma	0(0)	1(20)	
Neuroblastoma	2(25)	0(0)	
HCT			
Allogeneic	6(75)	4(80)	1
Auto	2(25)	1(20)	
CKRT			
CVVHD	3(37.5)	3(60)	0.5921
CVVHDF	5(62.5)	2(40)	
Intubation			
Yes	5(62.5)	5(100)	0.2308
No	3(37.5)	0(0)	
Inotropic support			
Yes	7(87.5)	4(80)	1
No	1(12.5)	1(20)	
Liberation			
Yes	4(50)	1(50)	1
No	4(50)	1(50)	
PRISM	11(7,15)	13(10,22)	0.3333
CKRT duration (d)	4(2,21)	4(2,7)	0.9775
Time from HCT to CKRT (d)	19.5(9,49)	28(22,88)	0.1368
IMV duration (d)	41(1,249)	7(3,44)	0.5952
AKI			
No/mild AKI	0(0)	3(60)	0.035
Severe AKI	8(100)	2(40)	

Values represented as N (%) or median (range)

ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; HCT, hematopoietic cell transplant; CKRT, continuous kidney replacement therapy; CVVHD, continuous veno-venous hemodialysis; CVVHDF, continuous veno-venous hemodiafiltration; PRISM, pediatric risk of mortality; IMV, invasive mechanical ventilation; AKI, acute kidney injury