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The role of continuous renal replacement therapy in the management of acute kidney injury associated with sinusoidal obstruction syndrome following hematopoietic cell transplantation

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Running title: Role of CRRT in AKI and SOS following HCT

Authorship Statement

All the authors are involved in all stages of the study and manuscript preparation.

Abstract

Background: Maintaining fluid balance pre- and post- myeloablative hematopoietic cell transplant (MA-HCT) is essential and usually requires frequent administration of diuretics. Hepatic sinusoidal obstructive syndrome is potentially life threatening, especially when associated with AKI and multi-organ failure. This study describes six patients who developed AKI-associated SOS and diuretic-resistant fluid overload who subsequently underwent continuous renal replacement therapy using standardized management guidelines for fluid balance post-HCT.

Materials and methods: Retrospective chart review of HCT patients between September 2011 and October 2013 at a tertiary care children's hospital.
Results: Thirty-four patients underwent MA-HCT in the study period. Six patients had SOS complicated by diuretic-resistant FO and underwent CRRT. Defibrotide was used in three patients. Median time on CRRT was 10.5 days. Sixty six percent (N=4/6) of patients had full resolution of SOS symptoms with mortality rate of 34% (N=2/6). Among patients who had full recovery of SOS symptoms, one patient developed AKI, end stage renal diseases and underwent kidney transplantation 34-months post-HCT.
Conclusions: Thus, out of 6 included patients, 2 died and 1 developed ESRD with only 50% (N=3/6) good outcome. Use of a standardized, evidence-based fluid-balance protocol and early initiation of CRRT for HCT related AKI/SOS was associated with good outcomes.

Key words:

Hematopoietic cell transplant; fluid overload; acute kidney injury; continuous renal replacement therapy; sinusoidal obstruction syndrome

Introduction

Acute kidney injury (AKI) is a common comorbidity in pediatric patients following hematopoietic cell transplantation (HCT), with an incidence ranging from 11-84% of these, 5-10% of patients may require renal replacement therapy (RRT). [1-3] Overall survival of children after HCT decreases significantly with increasing severity in AKI within the first 100 days post-HCT. [2, 3] Sinusoidal obstruction syndrome (SOS) is a potentially life-threatening, early post-HCT complication. [4] Although mild SOS resolves without long-term sequelae in most patients, SOS associated with multi-organ failure (MOF) has very high mortality rates, exceeding 80% despite aggressive supportive therapy.

Management of fluid balance is critical in the HCT patient. In particular, sodium and fluid restriction and diuretic use are cornerstones to the prevention of fluid overload in SOS-associated AKI. [5] Continuous renal replacement therapy (CRRT) has emerged as a treatment modality in critically-ill children with AKI and fluid overload (FO). [6] Standardized guidelines for initiating CRRT in the setting of SOS are not established.

Severe SOS requires a multidisciplinary approach for optimal patient outcomes. [5, 7] The Pediatric HCT, Nephrology and Critical Care teams developed institutional guidelines for managing AKI and FO in HCT patients. This report describes the index case that initiated the development of fluid management protocol attempting to standardize a clinical approach for five more patients who underwent CRRT as a supportive care modality in managing their severe SOS.

Materials and methods

Data for this report were obtained from a retrospective chart review of HCT patients between September 2011 and October 2013 at Rainbow Babies & Children's Hospital. All patients who developed SOS, diuretic-resistant fluid overload and AKI were included for further description. The University Hospitals Case Medical Center Institutional Review Board approved this study.

Definitions

Day of hematopoietic cell infusion was defined as day zero (D0). Baseline weight (kg) was defined as either the hospital admission weight (wt.) if the patient was admitted directly for transplant or the patient's weight on the first day of preparative conditioning regimen if the patient was admitted prior to HCT for any other medical reasons. Baseline height was the height used to calculate the body surface area (BSA) for dosing calculations related to HCT. Baseline serum creatinine (SCr) was defined as the lowest SCr in the three-month span preceding the start of conditioning regimen.

SOS was defined according to modified Seattle criteria; which are the presence of either hyperbilirubinemia (total bilirubin ≥2mg/dL) before post-transplant day 21, or tender hepatomegaly, weight gain (>5% from baseline) or ascites. [4,8]. When present, liver ultra-sound demonstrating reversal of portal venous blood flow was used in support of the diagnosis of SOS. AKI was defined and stratified using Kidney Disease: Improving Global Outcomes (KDIGO) Table 1 (2, 18).

Patients' fluid status was assessed by twice daily weight measurements, strict fluid input and output recordings, and daily renal function panel. Fluid overload was defined as the percentage of fluid accumulation by dividing the cumulative balance in

liters by patient's baseline weight and multiplying by 100%. We then used the cutoff value of >5% of fluid accumulation as a definition of fluid overload (16):

%FO (weight) =(Weight – Admit weight) x (Admit weight)$^{-1}$] x 100
%FO (input/output) =[(Total fluid input in liters–Total fluid output in liters)x(Admit weight)$^{-1}$] x100

Criteria for CRRT initiation included all the following: SOS, AKI-F, and diuretic-resistant FO >10% (16). CRRT was initiated within 8- 12 hours of SOS diagnosis. The diuretic resistance is defined as fluid retention (24 hours after initiation of Furosemide) despite the use of appropriate doses of frusemide in patient with FO>5%, with decreased renal function and clinical evidence of reduced and delayed peak concentrations of loop diuretics in the tubular fluid as evident by suboptimal urine output of less than 0.5 ml/kg/hr. after 4-6 hrs. of last frusemide infusion (16,17).

CRRT protocol

CRRT blood flow rates ranged from 4–5 ml/kg/min. Initial fluid removal rates were determined by the PICU and Nephrology physicians and adjusted as tolerated, ranging from 1-2 ml/kg/hr. Standard citrate anticoagulation was used to maintain post-filter ionized calcium (iCa) between 0.25 and 0.35 mmol/L and pre-filter iCa between 1.1 and 1.3 mmol/L. Replacement fluid calculated as follows (2000 ml/h x BSA) x $(1.73m^2)^{-1}$. In patients receiving defibrotide, efforts were made to keep INR <1.5 and platelets >30,000/mm^3.

Statistical Analysis

For all patients who underwent allogeneic or autologous HCT procedure as described above, medical records were used to abstract demographics, diagnoses, survival, clinical and laboratory data pertaining to markers of inflammation, as well as pulmonary, renal, cardiac, and hepatic function. Statistical analysis of specific comparisons between the two patient groups of survivors and non-survivors was performed using the two-sided Fisher's exact test. *P*-values less than 0.05 were regarded as significant.

Results

Thirty-four patients (age 1-26 years) received allogeneic (n=30) and autologous (n=4) HCT between September 2011 and October 2013. Thirty-one patients received single HCT; one patient with beta-thalassemia major underwent three matched unrelated donor (MUD) HCTs due to repeated graft failure; one patient with severe aplastic anemia underwent two MUD HCTs for primary graft failure; and one patient received two autologous tandem transplants for atypical Teratoid Rhabdoid tumor of the brain.

Fourteen patients had normal kidney function around engraftment period. Twenty patients (59%) developed AKI, further stratified according to AKI per KDIGO-AKIN guideline Stage I (8/20), Stage II (6/20) and stage III (6/20) occurring 14-60 days after the first HCT. Six patients fulfilled criteria for SOS (all had tender hepatomegaly, rapid weight gain and ascites) that was complicated by AKI (grade III AKI per KDIGO) and diuretic-resistant FO and subsequently received CRRT. All six patients received busulfan-based Myeloablative (MA) conditioning regimen; and busulfan doses were based on test-dose pharmacokinetics for all patients. Table 2 summarizes clinical demographics of this case series. The abdominal compartment pressures (measured <12 hrs.) at the initiation of CRRT are mentioned in Table 2.

Patient 1 (Index-case)

Two-year-old female who underwent MA-HCT for rare immune deficiency (Bare lymphocyte syndrome type 2) was diagnosed with SOS associated with hypotension and coagulopathy19 days following allogeneic HCT. Due to active hemorrhage, defibrotide was not administered. Her course was complicated by stage III AKI per KDIGO; and diuretic-resistant FO. She was started on CRRT when she reached 40% fluid overload (72 hours after reaching 10% fluid overload). Unfortunately, her clinical condition rapidly deteriorated to MOF, and she died 18 days after SOS diagnosis (D37 post-HCT).

Following this index case, an algorithm was developed to manage fluid overload in HCT patients (**Figure 1**). Five subsequent patients with SOS and stage III AKI: and

developed diuretic-resistant FO and were started on CRRT within 24 hours of meeting the criteria. Defibrotide was used in 3 patients. Reasons for not receiving defibrotide in the other patients were: unavailability of the drug (Patient 2) and retinal hemorrhage (Patient 6) (Table 2).

Median CRRT duration was 10.5 days and total CRRT days for all patients were 55 days. Citrate anticoagulation was well tolerated, and only one patient developed citrate gap, which resolved after adjusting citrate infusion rate. No side effects related to metabolic alkalosis, acidosis, or hypocalcemia were observed. No serious hemorrhagic events occurred. All five patients had complete resolution of SOS signs and symptoms as well as marked improvement in renal function, with 5 days' mean recovery time. One patient died on D97 post-HCT due to systemic Cytomegalovirus and Aspergillosis despite full recovery of renal function and SOS. Three of 5 patients had complete recovery of kidney function post-CRRT; one patient developed AKI-E and underwent kidney transplantation 34-months post-HCT (Patient-6) (Table 2). The overall length of stay (in days) in those without and with AKI for the whole cohort was 63.1 ± 47.3 vs. 86 ± 45.2 ($P<0.05$). The overall crude mortality of the patient who received allogeneic or autologous HCT without or with AKI was 0%vs.20% ($P< 0.05$).

Discussion

Incidence of AKI after HSCT ranges between 25-50%, and the incidence of renal replacement therapy (RRT) is 5-18%. In our cohort, 59% of patients developed AKI (14-60 days after HCT). Fluid overload (>20%) at the time of CRRT initiation, grade III AKI per KDIGO; and multisystem organ failure (>3 systems), were the risk factors associated with the mortality in these patients.

With increased applications of HCT for different disease indications, evaluation and treatment of HCT-related complications has become increasingly important to mitigate early transplant-related mortality and improve outcomes. [5, 8] SOS can be a devastating complication after HCT [4, 8]. Several studies have demonstrated that up to 50% of patients with SOS develop renal or pulmonary dysfunction [9]. Outcomes for these patients are poor as mortality rates reach as high as 84% by D100 post-HCT [10]. For patients who meet criteria for SOS (Baltimore or modified Seattle), supportive care efforts are centered on aggressive fluid management with special attention to

maintaining intravascular volume; so kidney perfusion is maintained. [5] In this regard, it is critical to avoid exacerbating AKI with aggressive diuresis or rapid removal of ascetic fluid. HCT recipients often require intravenous parenteral nutrition, frequent administration of blood products, and multiple nephrotoxic medications, all of which may worsen FO, further contributing to AKI [1, 2, 4, 8, 9]. Therefore, management of AKI and FO in HCT patients is particularly challenging; and when FO >20% or is refractory to conventional pharmaceutical diuresis, CRRT may need to be considered. This study showed that early initiation of CRRT and aggressive diuresis to prevent fluid overload seems to be necessary, but not sufficient for pediatric SCT patients with AKI. Also, early CRRT may blunt the inflammatory response and prevent need for intubation or increase likelihood of extubation. CRRT requires dialysis catheter placement, sedation and ICU care to monitor, prevent and manage potential hemorrhagic events that are inherent to SOS pathophysiology (refractory thrombocytopenia and coagulopathy due to hepatic dysfunction) and potentially associated with the use of defibrotide [10-12,16].
Our study was based on the initial publication by Goldstein et which showed that early initiation of diuretic in HCT (FO>5%) and or CRRT (FO>10%) prevents worsening of FO and may improve the survival (42%) of HCT patients with AKI. Using and implementing the algorithm in our cohort of HCT patients with SOS showed marked improvement in mortality from 90% to 50%. (13,16)

In our cohort of the patients who did not receive defibrotide, 1/3 was alive without ESRD. Of the patients who received defibrotide, 2/3 was alive without ESRD. One could argue that the use of defibrotide and not the CRRT protocol have been the cause of the better outcomes. However, defibrotide is the only available FDA approved therapy for SOS that is accompanied by either renal or pulmonary dysfunction after HCT. Yet not all patients can receive defibrotide in timely manner for medical reasons, including active bleeding, concomitant use of systemic anticoagulation or fibrinolytic therapy or known hypersensitivity to the drug. [10, 11] It is proposed that defibrotide is not the sole reason for improved outcome, but early CRRT/FO is a paramount for SOS treatment. Traditionally defibrotide has improved D100 post-HCT survival in patients with SOS and MOF with up to 40% of patients treated were on mechanical ventilation, dialysis or both at the time of drug initiation [10].

While defibrotide has emerged as a therapeutic option for many patients with SOS, managing fluid and acid-base balance in the context of AKI remains a significant challenge in pathogenesis of SOS. In our cohort the marked improvement in mortality from 90% to 34% is due to early recognition of patients at risk for development of AKI post-HCT transplant by way of standardized methods of staging and prevention of the occurrence of AKI is paramount to improve the outcomes of an otherwise life-saving therapy. Early initiation of CRRT may be a useful modality to prevent progressive fluid overload and maintain electrolyte and acid base balance in patients with FO and AKI following SOS.

Skeen's et al found significant variability in the diagnosis and management of SOS between HCT and Critical Care providers. [7]. The current work, presents our institutional experience with collaborative efforts between Pediatric HCT, Nephrology and Critical Care providers using a clinical evidence-based algorithm for fluid management and early CRRT initiation in pediatric HCT patients with SOS, AKI and FO (**Figure 1**). Following the unfavorable outcome of Patient 1 it instituted this standardized clinical approach to pediatric HCT patients with SOS-associated AKI and FO. Based on this approach, five subsequent patients were started on CRRT within 24 hours of meeting algorithm-based criteria. Following adoption of the algorithm, the observation of overall improvement in renal and liver functions in this cohort was realized. It is believed this outcome occurred because of adherence to the algorithm for fluid management and early CRRT initiation. In addition, it shows that regional citrate anticoagulation seemed to be safe form of anticoagulation in HCT patients with SOS, despite the potential risk of citrate toxicity associated with liver impairment. [13] None of the patients developed hemorrhagic events, metabolic acidosis, alkalosis, hypocalcemia or other electrolyte abnormalities. From this one can conclude that citrate anticoagulation is feasible and was not associated with apparent side effects in the population studied.

This study finds the incidence of AKI in the cohort to be high (59%), which may reflect the ability to identify patients with AKI using the KDIGO criteria, or prior fluid management approach.

Regarding the diagnosis of AKI, KDIGO agreed with pRIFLE /RIFLE 92% of the time. All three definitions correlate well with outcomes, however KDIGO was preferable

for AKI stage discrimination. pRIFLE used the Swartz formula but in this setting, a kinetic formula's that predicts true endogenous kidney function is needed, fluctuations in creatinine production, and fluid balance rather than steady-state GFR estimator (18). Measuring endogenous eGFR is expensive and complex, considerably outweighing their reliability and making them unsuitable for routine use in the patients with AKI following HCT. Authors feels AKIN has a ddiagnostic timeframe and more practical by using serum creatinine and urine output as a surrogate on daily basis rather that static eGFR which is dependent on heights or baseline creatinine values which are likely to be missing. Regardless of any definitions severe AKI is associated with higher mortality and longer length of stay in the ICU.

A new concept of renal angina index (RAI) to improve the prediction of acute kidney injury in critically ill children by Goldstein et al together with KDIGO classification and renal biomarkers may provide a clinically feasible and applicable methodology to identify HCT patient at risk of severe AKI lasting beyond functional injury. (16, 17) A unified AKI definition in subset of HCT cohort is needed and it is recommended by the authors that the nephrology and oncology community continue to work toward this goal.

Flores et al. used the Prospective Pediatric CRRT Registry to analyze 51 patients who underwent HCT and required CRRT. The authors noted that the %FO at CRRT initiation was relatively low (<12%) and similar between survivors and non-survivors, suggesting that increased mortality risk was related to factors other than excessive fluid accumulation. [14] By contrast, Sutherland et al. examined %FO at initiation of CRRT in 297 critically-ill children and demonstrated that fluid overload is independently associated with mortality. [15] These contradictory reports illustrate the paucity of data available regarding the optimal timing of CRRT. Wallhult et al. recently published the review for management of SOS utilizing a multidisciplinary approach to care. [5] This emphasized the role of nursing in early detection of the symptoms associated with SOS and timely treatment, with the goal of improving the outcome. [5] Intensive nursing with alleviating clinical barriers/efforts to get twice daily weights in the ICU setting, daily %FO calculation, strict intake and output charting including insensible loses should be incorporated into clinical care of patients with HCT. The authors concur with the guidelines and add to it our recommendation for early initiation of CRRT.

This analysis is limited by all the weaknesses inherent with a retrospective data collection and small number of patients. Clearly, prospective trial would appear indicated to confirm these findings.

Conclusion

Use of a standardized, evidence-based approach involving careful fluid management for patients undergoing HCT is essential. Early recognition of patients at risk for development of AKI post-transplant and prevention of the occurrence of AKI is paramount to improve the outcomes of an otherwise life-saving therapy. Renal support with early initiation of CRRT as an adjunct to enhance-renal function, modifying fluid balance (despite FO>20%), acid-base balance and control solute level may help in reducing mortality and morbidity of patients with FO and AKI following SOS. CRRT with citrate regional anticoagulation is safe and well tolerated in patients with SOS. Findings emphasize the need for multi-disciplinary approach to early recognition and management of AKI in patients with HCT-related SOS to improve outcomes (decreasing overall mortality from 90% to 50%). Nephrologists and Oncologists should work together to identify at risk patients and to prevent development of AKI by initiating therapy early to improve outcomes. Future large prospective studies are needed to confirm our findings.

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Table 1. The KDIGO classification/staging system of acute kidney injury [a]

Stage	SCr	UO
1	↑ SCr ≥26.5 µmol/L (≥0.3 mg/dL) or ↑SCr ≥150 a 200% (1.5 a 2×)	<0.5 mL/kg/h (>6 h)
2	↑ SCr >200 a 300% (>2 a 3×)	<0.5 mL/kg/h (>12 h)
3[b]	↑ SCr >300% (>3×) or if baseline SCr ≥353.6 µmol/L (≥4 mg/dL) ↑SCr ≥44.2 µmol/L (≥0.5 mg/dL)	<0.3 mL/kg/h (24 h) or anuria (12 h)

[a]SCr, serum creatinine; UO, urine output.

[b]Stage 3 also includes patients requiring RRT independent of the stage (defined by SCr and/or UO) they are in at the moment they initiate RRT.

Table 2 Patient Demographics

Variables	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age (years)/gender/ diagnosis	2/F/BLS-2	6/M/MDS	16/M/CML	12/F/AML	17/M/MDS	15/M/AML
Conditioning regimen	Bu/Cy/ATG	Bu/Cy	Bu/Cy/ATG	Bu/Cy/ATG	Bu/Cy/ATG	Bu/Cy/ATG
Stem cell source	BM	PBSC	CB	BM	PBSC	BM
SOS onset post HCT (days)	19	11	18	11	19	20
CRRT initiation after SOS diagnosis	72-96 hrs.	9 hrs.	10 hrs.	8.5 hrs.	11 hrs.	9.5 hrs.
%FO at the onset of CRRT	40	20	5	20	12	8
ACP at onset of CRRT	32	14	12	12	18	10
Defibrotide	No	No	Yes	Yes	Yes	No
Time to start Defibrotide after SOS diagnosis	-	-	24 hrs.	26 hrs.	20 hrs.	-
Total bilirubin/creatinine at initiation of CRRT (mg/dl)	14/3.1	1.8/0.63	6.3/1.52	1.6/1.23	8.3/1.45	3.2/2.15
CRRT duration (days)	0.5	6	9	15	12	12
CRRT Anticoagulation	Heparin	Citrate	Citrate	Citrate	Citrate/ Heparin	Citrate /Heparin
Outcome	Died (Day +37)	Alive	Alive	Alive	Died (Day +97)	Alive/ ESRD

AML: acute myeloid leukemia, ATG: anti-thymoglobulin, BLS-2: Bare lymphocyte syndrome type 2, BM: bone marrow, Bu: busulfan, ACP in mm (Normal <20mmHG) Abdominal Compartment Pressure, CRRT: continuous renal replacement therapy, CB: cord blood, CY: cyclophosphamide, F: female, MDS: myelodysplastic syndrome, M: male, PB: peripheral blood stem cells, SOS: sinusoidal obstruction syndrome

Figure 1. Algorithm to the management of fluid status in the patients undergoing hematopoietic cell transplant. The clinical algorithm that was developed after an index case (Patient 1 in **Table 2**).