A retrospective analysis of antithrombin III replacement therapy for the treatment of hepatic sinusoidal obstruction syndrome in children following hematopoietic stem cell transplantation

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Abstract

Hepatic sinusoidal obstruction syndrome (SOS) remains a serious complication of hematopoietic stem cell transplantation (HSCT). In this single institution retrospective case series, 18 children developed SOS after HSCT. Patients were treated with antithrombin III (AT III), defibrotide (DF), or ATIII followed by DF. Twelve out of 13 patients who were treated with ATIII therapy alone had complete resolution of SOS, including 4 out of 5 children with severe SOS. In this limited cohort, ATIII was safe and successfully prevented progression of hepatic SOS following HSCT in the majority of children at our center.

Keywords

Veno-occlusive disease; BMT; Stem Cell Transplantation; Sinusoidal obstruction syndrome; Antithrombin III

INTRODUCTION

Hepatic sinusoidal obstruction syndrome (SOS) is clinically characterized by fluid retention, weight gain, painful hepatomegaly and jaundice. Approximately half of the patients with SOS develop multiple organ dysfunction, and SOS carries a high risk of morbidity and mortality following hematopoietic stem cell transplantation (HSCT) [1, 2]. SOS usually presents within the first 21 days after HSCT [3, 4]. The incidence of SOS varies from 5% to as high as 60% [5–6]. The pathogenesis of SOS is from injury to hepatic venules and sinusoidal endothelium, ultimately leading to a localized hypercoagulable state and

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consumption of anticoagulants, especially antithrombin III (ATIII) [7–9]. In one large pediatric study, mortality in transplant patients at 100 days was greater in the VOD-positive group (38.5%) compared to the VOD-negative group (9.5%) [10].

Treatments for SOS have included ATIII, defibrotide (DF), and other fibrinolytic agents [11–13] but only DF has been recently FDA approved to treat adults and children with SOS after HSCT [14]. DF was not widely available for the patients included in this retrospective case series. There is limited data on the efficacy of ATIII for the treatment of SOS in children [15–17]. We therefore retrospectively reviewed our experience utilizing ATIII in children who developed SOS after HSCT.

MATERIALS AND METHODS

As a program evaluation, we conducted a retrospective analysis of 108 pediatric patients who had undergone HSCT (Table 1) at the University of Wisconsin, Madison between August 2003 to February 2015. There were 18 patients identified with a diagnosis of SOS. Conditioning regimens and donor sources varied (Table 2).

Diagnosis of SOS

We used the modified Seattle criteria [18] to diagnose hepatic SOS. The severity of SOS was classified retrospectively. Patients who had progressive SOS with ascites and/or pleural effusion were considered to have moderate SOS. Patients who required paracentesis, invasive pulmonary ventilation (including BiPAP), developed renal insufficiency defined as at least a doubling of serum creatinine from baseline, and /or developed encephalopathy not attributable to any other cause, were categorized as having severe SOS [18]. Complete resolution (CR) of SOS was defined as a resolution of fluid retention, weight gain, painful hepatomegaly, hyperbilirubinemia (bilirubin level < 2 mg/dL) and multiorgan dysfunction.

SOS Treatment Regimens

All 18 children received SOS prophylaxis, which was initiated on the day of admission and continued until day +30 or discharge, whichever came first. Fourteen children received both ursodiol and low dose heparin while 2 patients with history of recurrent epistaxis received ursodiol alone, and 2 patients, unable to tolerate ursodiol, received heparin alone. Those who fulfilled the diagnostic criteria of SOS were considered for therapy. Defibrotide was dosed at 6.25 mg/kg every 6 hours for 21 days. ATIII (Thrombate III, Grifols Inc., LA, California) was utilized off-label and dosed at 50 IU/kg IV every 8 hours for the first day, then 50 IU/kg IV every 24 hours thereafter based on prior studies [16,17]. Baseline ATIII levels were checked prior to initiation of ATIII therapy with a median ATIII level of 64% (range: 36% to 94%). Most of these patients received ATIII replacement therapy for 2–10 days (median 8 days). However, 3 patients received ATIII therapy more than 10 days (13, 14 and 24 days).

RESULTS

SOS Incidence and Severity

The overall incidence of SOS was 16.7%. The median time from transplant to diagnosis of SOS was 13 days (range: 5 to 20 days). The median peak total bilirubin was 6.8 mg/dL (range: 1.6 mg/dL to 39.1 mg/dL) and the median weight gain was 13% (range: 2% to 44%). Of the 18 patients diagnosed with SOS, 50% had mild-moderate SOS and 50% had severe SOS.

Treatment and Outcome

Among the 18 children who developed SOS, 13 (72%) received ATIII therapy alone, 2 (11%) received DF therapy alone, 2 (11%) patients received ATIII followed by DF, and 1 (6%) received no therapy for SOS (Table 1).

Of the 13 patients who received ATIII therapy alone, 12 (92%) had CR of SOS, with a median time from initiation of therapy to CR of 6 days. There were 5 patients in this group classified as having severe SOS, 4 of whom had CR of SOS and one of whom died of respiratory failure. The remaining 8 patients were classified as having mild-moderate SOS and all had CR of SOS. One patient who had a history of epistaxis prior to transplant developed epistaxis that required one dose of ATIII to be held. All remaining patients did not have bleeding complications.

Two severe SOS patients received ATIII therapy followed by DF. One patient was changed to DF after 5 days due to worsening SOS. This patient eventually died of multi-organ system failure. The second patient was transferred to a different center for DF therapy at the family's request. This patient experienced a CR and resumed post transplant care at our institution. Two patients who received DF therapy alone had severe SOS and died of multi-organ system failure and respiratory failure, respectively. The 1 patient with mild SOS who received no therapy for SOS had a CR.

The overall day +100 survival rates in patients with mild-moderate or severe SOS treated with ATIII replacement therapy alone were 100% and 80% (67% including the 1 patient who progressed on ATIII and received DF), respectively. No significant toxicities attributed to ATIII were observed.

DISCUSSION

The only FDA-approved therapy for SOS is DF, but was only approved in March 2016. ATIII had been utilized off-label as a therapy for SOS in pediatric HSCT patients, but very few efficacy data existed [15–17]. In 1997, Cincinnati Children's Hospital published their experience on the use of ATIII after treating 10 pediatric patients with severe post-HSCT organ dysfunction [16]. They noted that death due to SOS was significantly less in the ATIII treated group when compared to an historical control group receiving the same preparative regimen (25% vs 62%, $P = 0.047$). More recently, a retrospective study of 48 adult and pediatric patients who received ATIII for the treatment of SOS following HSCT was conducted by Peres et al [17]. They reported an 83% overall day +100 survival rate in

patients (both adults and children) with mild-moderate SOS and a 61% overall day +100 survival rate in patients with severe SOS. However, a subset analysis confined to pediatric patients was not performed in this study.

At our center, ATIII was utilized for the treatment of SOS in the majority of patients diagnosed with this complication as DF was not commercially available. Due to delays related to obtaining approval for DF on a compassionate use basis, patients receiving DF started 7 and 3 days after SOS onset compared to patients receiving ATIII, which was started within 0–3 days after SOS onset. The delay in initiating DF therapy suggests these patients had worse disease than those who received ATIII only, and early initiation of treatment is important to outcomes. A significant number of patients in our study with moderate SOS had CR, but it is possible that some of these patients would have done well with supportive measures alone. However in our experience, once patients develop severe SOS, spontaneous resolution is rare and so ATIII likely benefited these patients.

A major factor limiting use of ATIII is the cost. However, any cost analysis must also take into account the reduction of days spent in the hospital by successfully treating SOS and preventing a protracted stay in the Intensive Care Unit. The treatment course of ATIII is relatively short (2–10 days) in comparison to DF, which is usually administered for 21 days [14].

To our knowledge, this is the largest reported series focusing on the use of ATIII in a solely pediatric patient population with hepatic SOS. The CR rates for patients treated with ATIII alone, or ATIII in combination with (or followed by) DF were 92% and 87%, respectively. Importantly no significant toxicities attributed to ATIII were observed. Thus, in our retrospective case series, treatment with ATIII was shown to be safe and successfully prevented the progression of both moderate and severe hepatic SOS following HSCT in the majority of children. A larger prospective randomized multi-center trial will be needed to determine whether ATIII replacement therapy can be used as front line treatment for SOS, and to evaluate the cost of administering ATIII compared to other effective drugs, such as DF.

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TABLE 1

Treatment and outcomes of SOS patients

Median day of SOS onset	Day +13 (range: days 5 to 20)
Median baseline ATIII level (Normal: 85%–125%)	64% (range: 36% to 94%)
Total number of patients with SOS	18
a. Severe SOS	9
b. Moderate SOS	8
c. Mild SOS	1
Number of patients with and without therapy	
a. ATIII therapy alone	13 (72.2%)
b. DF alone	2(11.1%)
c. ATIII followed by DF	2 (11.1%)
d. No therapy	1 (5.6%)
Outcome	
Complete resolution of SOS	
a. ATIII therapy alone	12/13 (92%)
b. DF alone	0/2 (0%)
c. ATIII followed by DF	1/2 (50%)
d. No therapy	1/1 (100%)

TABLE 2

Patient characteristics and outcome

Patient	Age at BMT	Diagnosis	Type of transplant	Conditioning	Organ dysfunction	Other therapies	Type of treatment for SOS	Onset of organ dysfunction and dates of treatment	ATIII level pre-treatment %	Outcome of SOS
1	10Y	DSRCT	Auto PBSCT	Bu, Mel, Thiotepa	Moderate SOS	None	ATIII	+17/ +17 to +26	59	CR
2	10Y	Relapsed Hodgkin lymphoma	Mismatched UD BMT	Cy, TBI	Severe SOS, AKI (baseline Cr 0.7 to max Cr 3.0), AMS	HFNC	ATIII	+12/ +15 to +21	36	CR
3	8Y	DFA	MRD BMT	Bu, Flu, ATG	Moderate SOS	None	ATIII	+13/ +13 to +19 +22 to +29	77/09	CR
4	14mo	Atypical SCID	MRD BMT	Bu, Flu, ATG	Moderate SOS	None	ATIII	+15/ +15 to +21	94	CR
5	15Y	AML	MUD BMT	Bu, Flu, ATG	Moderate SOS	None	ATIII	+11/ +11 to +12	56	CR
6	5mo	Alpha thalassemia major	MUD BMT	Bu, Flu, ATG	Severe SOS, ARDS	Ventilator	ATIII	+13/ +13 to +36	53	CR
7	6mo	SCID	UC SCT	Bu, Flu, ATG	Severe SOS, pleural effusion	Bipap	ATIII	+16/ +16 to +22	59	CR
8	3Y	ALL	MUD BMT	Cy, TBI	Moderate SOS	None	ATIII	+17/ +17 to +19	77	CR
9	12Y	SAAS/SDS	Haplo-identical PBSCT	Bu, Flu, ATG	Severe SOS, ARDS, AKI (baseline Cr 0.5 to max Cr 2.8)	Ventilator CVVH	DF	+14/ +21 to +58	70	Died of multi-organ failure
10	16mo	AML	MRD BMT	Bu, Cy	Severe SOS, pleural effusion, AKI (baseline Cr 0.3 to max Cr 1.3)	Ventilator CVVH	DF	+14/ +17 to +34	61	Died of respiratory failure
11	16Y	ALL	MUD BMT	Cy, TBI, ATG	Severe SOS, ARDS, AKI (baseline Cr 0.7 to max Cr 4.7)	Ventilator CVVH	ATIII → DF	+16/ +16 to +20 → +21 to +33	64	Died of multi-organ failure
12	6Y	JMML	MRD BMT	Bu, Mel, Cy	Mild SOS	None	None	+11	n/a	CR
13	2Y	SCD	MRD BMT	Bu, Flu, ATG	Severe SOS, Ascites	Peritoneal drain	ATIII	+20/ +20 to +32	n/a	CR
14	7mo	JMML	MUD BMT	Bu, Flu, Mel	Moderate SOS	NC	ATIII	+9/ +10 to +12	94	CR
15	4Y	Ph+ ALL	MRD BMT	Cy, TBI	Moderate SOS	None	ATIII	+18/ +18 (one dose)	76	CR
16	4Y	Relapsed Neuroblastoma	Haplo-identical PBSCT	Flu, Thiotepa, ATG	Severe SOS, AKI (baseline Cr 0.41 to max Cr 0.83)	None	ATIII transferred to different institution for DF	+5/ +5 to +9 (until transferred)	61	CR
17	1Y	Infant ALL (MLL-R)	MUD BMT	Bu, Flu, ATG	Severe SOS, ascites, AKI (baseline Cr 0.3 to max Cr 1.7)	Ventilator	ATIII	+10/ +16 to +17	n/a	Died of respiratory failure

18	5mo	SCID	UC SCT	Bu, Flu, ATG	Moderate SOS, ascites, pleural effusion	None	ATIII	+17/ +18 to +25	68	CR
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AKI = acute kidney injury, ALL = acute lymphoblastic leukemia, AML = acute myelogenous leukemia, AMS = altered mental status, ARDS = acute respiratory distress syndrome, ATG= antithymocyte globulin, BMT = bone marrow transplant, Bu = Busulfan, CR = complete response, Ct= creatinine, Cy = cyclophosphamide, CVVH = central veno-venous hemofiltration, DFA = Diamond Blackfan anemia, DSRCT = desmoplastic small round cell tumor, Flu = fludarabine, HFNC = high flow nasal cannula, JMML = juvenile myelomonocytic leukemia, Mel = melphalan, MRD = matched related donor, MUD = matched unrelated donor, PBSCT = peripheral blood stem cell transplant, Ph = Philadelphia chromosome, SAA= severe aplastic anemia, SCD= sickle cell disease, SCID = severe combined immunodeficiency, SDS = Schwachman Diamond syndrome, SOS = sinusoidal obstruction syndrome, TBI = total body irradiation, UC = umbilical cord, UD = unrelated donor