Evaluation of defibrotide use in an academic pediatric institution

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Background

Sinusoidal Obstructive Syndrome (SOS)[1]:

- SOS, also known as veno-occlusive disease, is a severe potential complication of blood and bone marrow transplantation (BMT)
- Endothelial damage often caused by toxic injury from chemotherapy creates gaps in the sinusoidal barrier, allowing for extravascular deposition of red blood cells, leukocytes, and other debris, leading to a prothrombotic state
- SOS has been associated with upwards of 80% mortality
- Initially, SOS often presents as hyperbilirubinemia, ascites, otherwise unexplainable weight gain, and hepatomegaly
- Two current diagnostic criteria exist: Baltimore Criteria and Seattle Criteria, both for adults
- The European Society of Bone and Marrow Transplantation (EBMT) have proposed distinct criteria for use in pediatric populations
- The only treatment for SOS was symptom management until 2016

Defibrotide:

- Defibrotide was FDA approved in March 2016, for use in adults and children with renal or pulmonary dysfunction post-BMT
- Defibrotide helps restore the thrombotic-fibrinolytic balance and protect endothelial cells, lowering SOS related mortality and improving symptoms
- Standard treatment consists of 84 doses divided every 6 hours over the course of 21 days
- Children's Mercy Kansas City started using defibrotide in 2016 for the treatment of SOS post-BMT

Objectives

Primary:

- To characterize defibrotide use at Children's Mercy Kansas City

Secondary:

- To describe patient outcomes of defibrotide use at Children's Mercy Kansas City

Methods

- Retrospective chart review of patients who received defibrotide at Children's Mercy Kansas City between April 1, 2016 and September 30, 2019
- Excluded investigational defibrotide use
- Approved by Institutional Review Board

Table 1. SOS Diagnostic Criteria[2]

Criteria:	Seattle	Baltimore	Proposed EBMT
Time Frame:	First 20 days after BMT, ≥ 2 of the following:	First 21 days after BMT, >2mg/dL bilirubin plus ≥ 2 of the following:	≥ 2 of the following with no limitation for the time of onset:
Hepatomegaly	X	X	X
Bilirubin > 2mg/dL	X	X	X
Weight gain (>5% basal weight)	X	X	X
Ascites		X	X
Refractory thrombocytopenia			X
3 consecutive days of bilirubin rise			X

Participants

Table 2. Patient Characteristics

Total participants screened, N	18
Total participants included, N	14
Indication for Transplant, N • Leukemia • Neuroblastoma • Beta-thalassemia • Severe Combined Immunodeficiency	 7 4 2 1
SOS diagnosis, N	11
Received defibrotide as prophylaxis, N	3
Received myeloablative conditioning, N	11
Age in years, median (range)	6.83 (0–11)
Female, N (%)	7 (50)
Time to defibrotide initiation in days, median (range)	16 (-8–178)
Duration of treatment in days, median (range)	20.5 (3–21)

Results

Fig. 1: Criteria Met for SOS Diagnosis

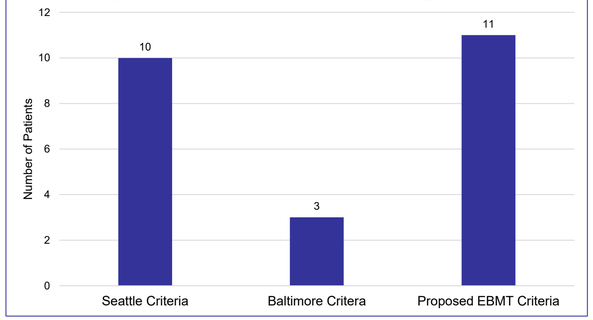


Fig. 2: Specific Diagnostic Criteria Met

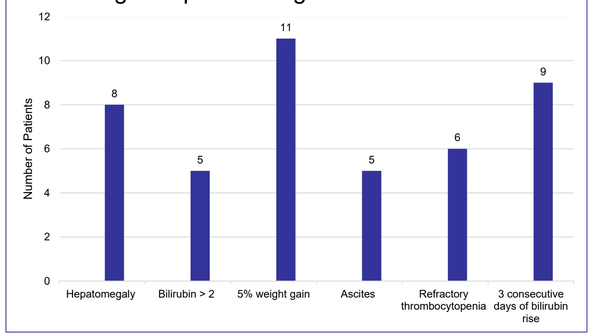
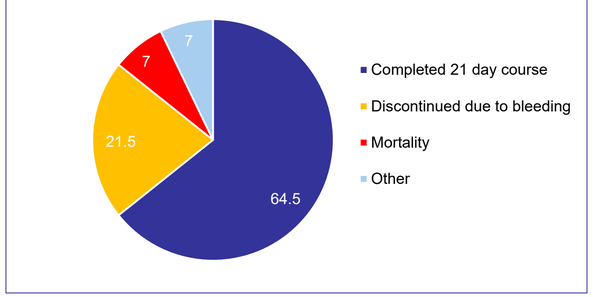


Fig. 3: Patient Outcomes (N = 14)



Discussion

- All patients diagnosed with SOS met proposed EBMT pediatric criteria compared to only 90% and 28% for the Seattle and Baltimore criteria, respectively
- The inclusion of a trend in bilirubin levels rather than a single value likely contributed to the increased diagnosis of SOS with the proposed EBMT criteria
- Ascites and bilirubin ≥ 2 mg/dL occurred less frequently than other diagnostic markers
- Three patients (21%) were treated prophylactically and therefore, were not assessed with the diagnostic criteria
- Two patients received prophylaxis due to prior SOS diagnoses, and one patient received prophylaxis due to high risk at time of transplantation

Conclusion

- Not all SOS diagnostic criteria can be applied equally within a pediatric population
- Pediatric specific criteria proposed by the EBMT accurately diagnosed the highest proportion of patients being treated for SOS

Future Directions

- Further prospective research studies are warranted to test the sensitivity and specificity of diagnostic criteria for SOS in a pediatric population as well as to determine specific risk criteria for the initiation of defibrotide prophylaxis.

References

1. Corbacioglu S, Jabbour EJ, Mohty M. Biol Blood Marrow Transplant. 2019;25:1271-80
2. Kammersgaard MB, Kielsen K, Heilmann C, et al. Bone Marrow Transplantation. 2019;54:1406-18

Disclosures

The authors of this presentation have nothing to disclose concerning possible financial or personal relationships with commercial entities that may have a direct or indirect interest in the subject matter of this presentation.