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Identification of Pediatric Stem Cell Transplant Patients at High Risk for Hepatic Veno-Occlusive Disease

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Introduction

- Veno-occlusive disease (VOD) is a rare but serious complication that may lead to multi-organ dysfunction/failure
- In the United States, defibrotide is the only approved agent for the treatment of VOD; however, there are no indications for prophylactically treating patients with high risk factors
- In an effort to decrease VOD incidence, the British Society for Blood and Marrow Transplant (BSBMT) has released guidelines on prophylaxis with defibrotide

Prophylactic Criteria

Patients are prophylactically treated if they have one of the following risk factors:

- Busulfan-containing conditioning
- Pre-existing hepatic disease
- Previous myeloablative transplant
- Prior treatment with gemtuzumab ozogamicin
- Allogeneic transplant for leukaemia beyond second relapse
- Diagnosis of primary haemophagocytic lymphohistiocytosis (HLH), andrenoleucodystrophy, or osteopetrosis

Objective

The purpose of this study was to:

- Analyze patients who were diagnosed with VOD and determine if they met the criteria for defibrotide prophylaxis as stated by the BSBMT
- Identify additional risk factors for developing VOD
- Analyze diagnostic criteria and characteristics of patients diagnosed with VOD

Methods

- A single center, retrospective chart review
- Inclusion criteria
  - Any patient treated for hematopoietic cell transplant at Cardinal Glennon Children's hospital from January 1, 2010 through May 6, 2019

Data collected:

- Demographics (age on day of transplant, gender, diagnosis, and weight)
- Transplant Characteristics (stem cell transplant source, donor source, admission date, and transplant date)
- Possible VOD risk factors (presence of baseline liver disease, history of liver fibrosis, underlying malignancy, history of gentuzumab/inotuzumab, prior abdominal radiation, Karnosky index <90%, previous myloablative hematopoietic cell transplant, conditioning regimen, administration of busulfan and cyclophosphamide, oral busulfan, and total body irradiation)
- Lab Values (serum creatinine, total bilirubin, direct bilirubin, AST, and ALT)
- VOD Characteristics (day of diagnosis, diagnostic criteria met, hepatic venous Doppler diagnosis, TPN and lipid use, treatment, outcome, and number of hepatotoxic medications of day of diagnosis)

Results

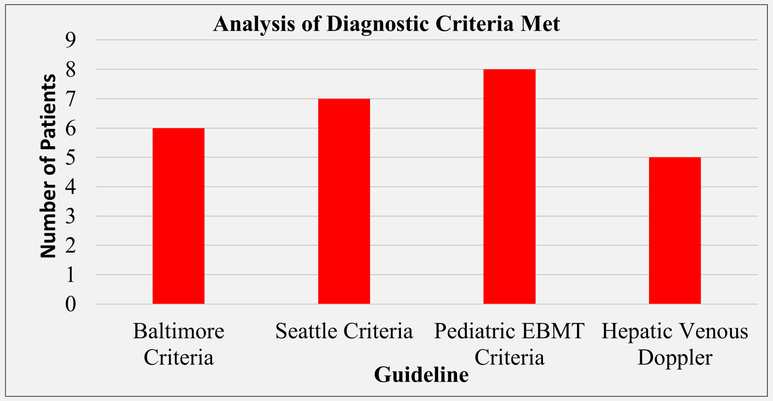
Patient demographics	Overall N=74 N (%) or Mean (Quartile range)	Patients who developed VOD N=8	Patients who did not develop VOD N=66
Age on day of transplant (months)	103.6 (27.3-180.5)	24.5 (4.5-36.35)	113.2 (35.5-192.8)
Gender, Male	40 (54.1%)	5 (62.5%)	36 (54.5%)
Admit Weight (kg)	37 (13.2-54.8)	11 (6.0-14.1)	40 (14.8-56)
Diagnosis			
-Severe Combined Immunodeficiency (SCID)	4 (5.4%)	2 (25%)	2 (3.3%)
-Solid Tumor	18 (24.3%)	2 (25%)	16 (24.2%)
-Myeloproliferative Disease	5 (6.8%)	4 (50%)	1 (1.5%)
-Other	47 (63.5%)	0 (0%)	44 (72.7%)

Transplant Characteristics/Possible VOD Risk Factors	Overall N=74	Patients who developed VOD N=8	Patients who did not develop VOD N=66
Stem Cell Transplant Source			
-Peripheral Blood	37 (50%)	2 (25%)	35 (53.0%)
-Umbilical Cord Blood	19 (25.7%)	6 (75%)	13 (19.7%)
-Marrow	18 (24.3%)	0 (0%)	18 (27.3%)
Donor Source			
-Autologous	34 (45.9%)	2 (25%)	32 (48.5%)
-Allogeneic Matched Related Donor (Allo-MRD)	14 (18.9%)	1 (12.5%)	13 (19.7%)
-Allogeneic Matched Unrelated Donor (Allo-MUD)	23 (31.1%)	4 (75%)	19 (28.8%)
-Allogeneic Matched Unrelated Donor (Allo-MMUD)	3 (4.1%)	1 (12.5%)	2 (3.0%)
Baseline Liver Disease	1 (1.3%)	1 (12.5%)	0 (0%)
History of Liver Fibrosis	47 (63.5%)	5 (62.5%)	42 (63.64%)
Underlying Malignancy	58 (78.4%)	6 (75%)	52 (78.8%)
History of Gemtuzumab/ Inotuzumab	1 (1.4%)	0 (0%)	1 (1.52%)
Prior Abdominal Radiation	15 (20.3%)	0 (0%)	15 (22.7%)
Karnofsky Index <90%	24 (32.4%)	1 (12.5%)	23 (34.8%)
Previous Myloablative HSCT	12 (16.2%)	1 (12.5%)	11 (16.7)
Conditioning Regimen			
-Bu/CTX/ATG*	10 (13.5%)	2 (25%)	8 (12.1%)
-Bu/Mel*	12 (16.2%)	2 (25%)	10 (15.2%)
-Bu/CTX/Mel/ATG*	5 (6.8%)	4 (50%)	1 (1.5%)
-Other	47 (63.5%)	0 (0%	47 (71.2%)
Bu-CTX*	16 (21.6%)	6 (75%)	10 (15.2%)
Oral Bu	0 (0%)	0 (0%)	0 (0%)
Total Body Irradiation	13 (17.6%)	0 (0%)	13 (19.7%)

* Bu (Busulfan), CTX (Cyclophosphamide), ATG (Antithymocyte Globulin), Mel (Melphalan)

Baseline Lab Values	Overall N=74	Patients who developed VOD N=8	Patients who did not develop VOD N=66
Baseline Serum Creatinine (mg/dL)	0.47 (0.28-0.60)	0.29 (0.21-0.38)	0.49 (0.29-0.61)
Baseline Total Bilirubin (mg/dL)	0.44 (0.3-0.5)	0.49 (0.23-0.75)	0.43 (0.3-0.5)
Baseline Direct Bilirubin* (mg/dL)	0.17 (0.1-0.21)	0.30 (0.18-0.42)	0.16 (0.1-0.19)
Baseline AST	35.3 (22.0-40.5)	40.5 (24-60)	34.6 (22-40)
Baseline ALT	31.7 (17-43.3)	26.9 (15-43.25)	32.3 (17-43)

VOD Characteristics	Overall N=8
Diagnosis on Day + ___ of Transplant	18.8 (10-19.5)
TPN and Lipids Prior to Diagnosis	7 (87.5%)
Hepatotoxic medications (# on day of diagnosis of VOD)	2.6 (2-3)
Treatment with Defibrotide	7 (87.5%)



Limitations

- There were 74 different transplants analyzed, but only 64 total patients. Therefore, multiple data analysis points may have been from the same patient but during a different transplant
- The EHR only dated back to 2010, so any data collected before that timeframe could not be analyzed
- Most patients receiving a transplant before 2012 did not have detectable or accurate direct bilirubin values

Discussion

- The number of patients needed to show a possible prophylactic benefit of defibrotide was 2
- All 8 patients with VOD were indicated for prophylaxis
- 36 (54.5%) patients did not develop VOD and were indicated for prophylaxis
- 100% of the patients who developed VOD had Busulfan in their conditioning
- 50% of patient with SCID developed VOD along with 80% of patients with myeloproliferative disease
- 32% of patients who received an umbilical cord transplant developed VOD
- 19% of transplants with an unrelated donor resulted in VOD
- Gemtuzumab exposure and previous myloablative HSCT was not significantly different between the two groups
- All laboratory values were balanced between the two groups
- The average day of diagnosis was day +18 of transplant
- Total mortality of the VOD group was 25%
- EBMT criteria was the only diagnosis criteria every VOD patient met

Conclusion

- Health care providers can appropriately predict if a patient is at high risk for developing veno-occlusive disorder
- Utilizing the BSBMT guideline recommendations, patients at risk for developing VOD should be prophylactically treated before liver damage becomes too prominent
- Health care providers should use the EBMT diagnostic criteria when diagnosing VOD since it is the most inclusive