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Eculizumab Therapy in Children with Severe Hematopoietic Stem Cell Transplantation–Associated Thrombotic Microangiopathy

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A B S T R A C T

We recently observed that dysregulation of the complement system may be involved in the pathogenesis of hematopoietic stem cell transplantation–associated thrombotic microangiopathy (HSCT-TMA). These findings suggest that the complement inhibitor eculizumab could be a therapeutic option for this severe HSCT complication with high mortality. However, the efficacy of eculizumab in children with HSCT-TMA and its dosing requirements are not known. We treated 6 children with severe HSCT-TMA using eculizumab and adjusted the dose to achieve a therapeutic level >99 μg/mL. HSCT-TMA resolved over time in 4 of 6 children after achieving therapeutic eculizumab levels and complete complement blockade, as measured by low total hemolytic complement activity (CH50). To achieve therapeutic drug levels and a clinical response, children with HSCT-TMA required higher doses or more frequent eculizumab infusions than currently recommended for children with atypical hemolytic uremic syndrome. Two critically ill patients failed to reach therapeutic eculizumab levels, even after dose escalation, and subsequently died. Our data indicate that eculizumab may be a therapeutic option for HSCT-TMA, but HSCT patients appear to require higher medication dosing than recommended for other conditions. We also observed that a CH50 level ≤ 4 complement activity enzyme units correlated with therapeutic eculizumab levels and clinical response, and therefore CH50 may be useful to guide eculizumab dosing in HSCT patients as drug level monitoring is not readily available.

INTRODUCTION

Hematopoietic stem cell transplantation–associated thrombotic microangiopathy (HSCT-TMA) is a challenging post-transplant complication associated with long-term morbidity and high mortality [1-3]. HSCT-TMA shares features with other TMAs where endothelial injury affects the kidney and other organs. Mild HSCT-TMA may have a benign course that requires no therapy or only modification of calcineurin inhibitor dosing [4,5]. However, a proportion of cases develop a systemic vascular injury that manifests as kidney damage, serositis, pulmonary hypertension, and multisystem organ failure [6-9]. In the most severe form of HSCT-TMA, mortality rates approach 90%, whereas milder cases have an increased risk of chronic kidney disease [3,8,10]. Targeted therapy is urgently needed for patients with severe HSCT-TMA in whom mortality is the highest.

Recently, we showed that patients with HSCT-TMA have evidence of complement dysregulation, including complement factor H autoantibodies and renal C4d deposition [11,12]. HSCT-TMA is a multifactorial disease in which either the classical or alternative complement pathways may become activated, resulting in tissue damage from microvessel thrombosis [13]. Currently available therapeutic options in patients with HSCT-TMA include therapeutic plasma exchange (TPE), rituximab, and withdrawal of calcineurin inhibitors. However, clinical response is often limited, especially in patients with severe HSCT-TMA. Furthermore, altering immunosuppressive therapy may increase the risk of graft-versus-host disease (GVHD), which itself is associated with high mortality [5,14,15].

Eculizumab, a humanized monoclonal antibody against the complement component C5 that prevents tissue damage by blocking formation of the membrane attack complex, is increasingly prescribed in the treatment of other diseases presenting with TMA [16-19]. Eculizumab has a low toxicity profile and has been well tolerated in patients with

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Table 1
Patient Demographics and Disease Characteristics

	Responders				Non-responders	
	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Gender	F	F	M	F	M	M
Age at HSCT, y	4.9y	5.1y	2.4y	4.3y	7.2y	10.9y
Weight, kg	4.9	5.1	2.4	4.3	7.2	10.9
Diagnosis	NBL	NBL	WAS	CID	WAS	CID
Stem cell source	Autologous	Autologous	Allogeneic	Allogeneic	Allogeneic	Allogeneic
HSCT conditioning regimen	MA	MA	MA	RIC	MA	RIC
Day post-HSCT when TMA was diagnosed	13	68	390	6	41	57
Cystatin C-eGFR (mL/min) at TMA diagnosis	48	20	16	30	15	17
Renal replacement therapy at TMA diagnosis	No	No	Yes	No	No	Yes
Urine protein-to-creatinine ratio (normal <.2 mg/mg, nephrotic >2 mg/mg)	81.6	11.3	4.5	10.6	14.1	6.4
HSCT-TMA–related complications	HTN, PH, pericardial effusion	HTN, pericardial effusion	HTN, pericardial tamponade	HTN, PRES, seizures, pericardial effusion	HTN, pulmonary bleeding	HTN, pericardial effusion
Complement profile*	↑C2, ↑C6, ↑CFB	↓C4	↓C4	↑C5, ↑C7, ↑C4BP	↑ C8, ↑C1Inhib, ↓ CFH	↑ C1Q, ↑C4, ↑C8
sC5b-9 (normal, 119 to 17 5 ng/mL)	283	307	139(on TPE)	328	432	375
CFH antibody	Absent	Absent	Absent	Absent	Absent	Absent
CFHR3-CFHR1 (by MLPA)	Not tested	Normal	Heterozygous deletion	Normal	Not tested	Not tested
CFHR1 protein	Present	Present	Present	Present	Present	Present
Renal biopsy/autopsy	Not done	TMA, C4d deposits in arterioles	Not done	Not done	Not done	TMA
Infections	None	None	None	None	None	Adenovirus, BK, and HSV viremia
Acute GVHD	n/a	n/a	Yes (skin)	No	Yes (skin, gut)	Yes (skin, gut)
Eculizumab start from HSCT-TMA diagnosis, days	3	40	122	26	24	97
Number of eculizumab doses given	9	13	6	4	7	2
Number of TPE sessions done before starting eculizumab	None	32	79	15	24†	17†

NBL indicates neuroblastoma; WAS, Wiskott-Aldridge syndrome; CID, combined immunodeficiency; MA, myeloablative regimen; RIC, reduced intensity regimen; HTN, systemic hypertension; PH, pulmonary hypertension; PRES, posterior reversible encephalopathy syndrome; HSV, herpes simplex 1 virus; MLPA, multiplex ligation-dependent probe amplification; Del (CFHR3-CFHR1), heterozygous deletion of CFH gene 3 and 1; n/a, not applicable.

* Complement profile includes C1inhib, complement component 1 inhibitor; C1Q, complement component 1q complex; C2-C9, complement components 2-9; C4BP, C4d binding protein; complement factors (CF) F, B, H, and I.

† Died while on eculizumab therapy.

paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome (aHUS). It has been approved for use in children with aHUS, and a pediatric weight-based dosing schedule has been established [20]. It is unknown if eculizumab is effective in children with HSCT-TMA and if the existing dosing regimen adequately blocks complement in these patients. Therefore, we describe our clinical experience in a cohort of children treated with eculizumab for severe HSCT-TMA and propose an algorithm to adjust the dosage and monitor therapeutic response based on our observations.

METHODS

Patient Population

Six patients with severe HSCT-TMA were treated with eculizumab (Alexion, Cheshire, CT) at Cincinnati Children's Hospital Medical Center (CCHMC) between January 2012 and May 2013. The CCHMC Institutional Review Board approved retrospective chart review. Patient demographics, therapy characteristics, and HSCT complications were abstracted from the medical record. HSCT-TMA was diagnosed using current diagnostic criteria and included elevated lactate dehydrogenase above normal for age, haptoglobin below the lower limit of normal, schistocytes on peripheral blood smear, anemia, thrombocytopenia, a negative Coombs test, and acute kidney injury, defined as a doubling of the serum creatinine or a 50% decline in the cystatin C–estimated glomerular filtration rate (eGFR) from each subject's pre-HSCT baseline [5,21,22]. Proteinuria was identified using a random spot urine protein-to-creatinine ratio (normal <.2 mg/mg, nephrotic range >2 mg/mg) [23,24]. Kidney biopsy results, if available, were reviewed for histology of TMA.

Each subject's legal guardian signed informed consent for treatment with eculizumab. The decision to start eculizumab was at the discretion of the treating physician but generally included severe TMA presenting with multiorgan impairment, uncontrolled hypertension, worsening renal function, and a lack of response to TPE and withdrawal of calcineurin inhibitors in allogeneic transplant recipients.