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Thrombotic Microangiopathy Following Pediatric Autologous Hematopoietic Cell Transplantation: A Report of Significant End-Organ Dysfunction in Eculizumab-Treated Survivors

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Abstract

Transplantation-associated thrombotic microangiopathy (TA-TMA) is a known complication of autologous hematopoietic cell transplantation (aHCT), particularly in children with neuroblastoma. We describe a pediatric single-institution experience of TA-TMA after aHCT. Data were abstracted from the medical record of patients who underwent aHCT between January 1, 2008, and July 1,2018, at Boston Children's Hospital. TA-TMA was diagnosed using either the International Working Group criteria or the "probable TA-TMA criteria" of Cho et al. Overall, 318 aHCTs were performed in 243 patients. Nine patients (3.7%) were diagnosed with TA-TMA. TA-TMA occurred most frequently in children with neuroblastoma (n = 7; 78%), all of whom were conditioned with carboplatin, etoposide, and melphalan. The median age at aHCT in children who developed TA-TMA was 3 years, 5 months (range, 18 months to 25 years). TMA was diagnosed at a median of 35 days (range, 8 to 106 days) after stem cell infusion. On a retrospective chart review using the same criteria used by the provider, patients met criteria a median of 5 days before the clinical diagnosis (range, 0 to 58 days). Eight patients had renal involvement at presentation, including nephrotic range proteinuria and severe hypertension, requiring from 2 to 6 antihypertensive medications. Two patients presented with multiorgan failure. Six patients were treated with eculizumab a median of 0 days after TA-TMA diagnosis (range, 0 to 11 days). On retrospective review, patients were treated a median of 18 days (range, 0 to 58 days) after meeting criteria for TA-TMA. Before initiation of therapy, 4 of 6 patients checked for serum complement levels had normal values, 1 had elevated CH50 and 1 had elevated sC59-b and CH50. All patients had CH50 levels within the target range (≤3 CAE) after induction therapy. Two patients (33%) had no response to eculizumab and died of multiorgan failure. The other 4 had both a hematologic response with transfusion independence (median, 6.5 weeks; range, 4 to 9 weeks) and renal response, defined as resolution of nephrotic range proteinuria (median, 21 weeks; range, 13 to 25 weeks). Among the eculizumab-treated survivors, 2 patients remained on prolonged eculizumab therapy, and one had recurrence of TA-TMA after discontinuation of eculizumab. All 4 eculizumab treated survivors have persistent organ dysfunction. Three children were treated with

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supportive care only; 2 died of relapsed cancer, and the third is alive with stage 2 chronic kidney disease. The median duration of follow-up after TA-TMA diagnosis was 2.5 years (range, 9 months to 4 years). The 1-year overall survival was 78% (SE = 14%). However, regardless of treatment, no survivors had complete normalization of function in all organs. Two children with normal serum CH50 and sc5b-9 levels responded to eculizumab. This report highlights the importance of maintaining a high suspicion for TA-TMA after aHCT. Further study is warranted to identify individual risk factors for TMA after aHCT, predict the response to eculizumab, and capture long-term sequelae in survivors.

Keywords

Autologous hematopoietic cell transplantation; Neuroblastoma; Transplant associated thrombotic microangiopathy; Eculizumab; Chronic kidney disease

INTRODUCTION

Transplantation-associated thrombotic microangiopathy (TA-TMA) is a known complication of hematopoietic cell transplantation (HCT). Although TMA is more frequently described after allogeneic HCT, it is being increasingly reported in the setting of autologous HCT (aHCT) as well [1–3]. Risk factors for TA-TMA after allogeneic HCT include conditioning regimen intensity and infections [4–6]. Clinical manifestations vary, although multiorgan failure and death are reported in approximately 50% of patients. Proteinuria (>30 mg/dL) and evidence of terminal complement activation (elevated serum sC5b-9) at diagnosis are considered high-risk features associated with a 1-year overall survival rate of <20% [7].

Far less is known about TA-TMA after aHCT. In children, TA- TMA has been described only after aHCT for neuroblastoma [1,2]. In a retrospective study of children with neuroblastoma, the prevalence rate of TA-TMA was 20% [2]. Of those with TA-TMA, 21% (13 of 60) presented with multiorgan failure, suggesting that clinically significant TA-TMA is not rare in the autologous setting [2]. Conditioning with carboplatin, etoposide, and melphalan is an identified risk factor in this population [1,2].

The pathophysiology of TA-TMA is thought to involve dysregulation of the complement alternative pathway in the setting of endothelial injury from chemotherapy, infection, and/ or inflammation [8–10]. Alterations in complement sC5b-9 at TA-TMA diagnosis are described in both autologous and allogeneic HCT [11,12]. Eculizumab, a monoclonal antibody to C5, is highly effective and has received Food and Drug Administration approval to treat other complement-mediated diseases, including atypical hemolytic uremic syndrome (aHUS) and paroxysmal nocturnal hemoglobinuria. Eculizumab has been used in TA-TMA in both allogeneic HCT and aHCT. There is no standard definition of response to eculizumab. Previous studies have defined a hematologic response as transfusion independence and defined resolution of schistocytes and renal response as improvement in proteinuria to values below the nephrotic range, a protein-to-creatinine ratio <2 mg/mg [13]. In the TA-TMA setting, reported response rates to eculizumab range from 60% to 70% in pediatric patients, with a median time to hematologic response of 36 days and a median time

to renal response of 46 days [8,13]. Patients who do not respond often die of multiorgan failure [13].

Unlike in aHUS, the endothelial injury in TA-TMA is expected to resolve over time without a need for ongoing therapy, and eculizumab has successfully been discontinued after TA-TMA in multiple studies [13,14]. The optimal dosing and duration of treatment are unclear. Standard eculizumab administration is weekly for 4 weeks with dose adjustments made to maintain a CH50 level of 0 to 3 complement activity enzyme (CAE) [12,13]. When the hematologic signs of TA-TMA have resolved, it is recommended that therapy be transitioned to every 2 weeks (maintenance therapy) for an additional 4 weeks with an adequately suppressed CH50 level of ≤3 CAE [8]. If there are no signs of microangiopathy, then eculizumab can be stopped. To our knowledge, there have been no previously reported cases of recurring TMA after therapy completion. Here we report a single-institution experience of TA-TMA occurring in children after aHCT.

METHODS

In this Institutional Review Board-approved retrospective study, we identified all patients diagnosed with TA-TMA after aHCT between January 1, 2008, and July 1, 2018 at Dana-Farber/Boston Children's Cancer and Blood Disorders Center. Using departmental records, a list of all patients who received cellular therapy and had a billing code at any time point for TMA, aHUS, or thrombotic thrombocytopenia purpura were identified. Medical records were then reviewed, and patients who were diagnosed with TA-TMA by an attending HCT physician were included in the study.

Before 2010, providers diagnosed TA-TMA using International Working Group (IWG) criteria: the presence of schistocytes, a sudden and persistent increase in lactate dehydrogenase (LDH), thrombocytopenia, decreased hemoglobin or increased transfusion needs, and decreased haptoglobin [15]. After 2010, the "probable TA-TMA criteria" from Cho et al [16] was used for diagnosis: LDH above the upper limit of normal for age, de novo thrombocytopenia with a platelet count $<50 \times 10^9$/L or a ≥50% decrease in platelet count, de novo anemia with a hemoglobin below the lower limit of normal or requiring transfusion support, microangiopathic changes with schistocytes in the peripheral blood or histological evidence of microangiopathy on a tissue specimen, and absence of coagulopathy and a negative Coombs test. Schistocytes in the peripheral blood are reported by a hematology laboratory technician. Confirmatory manual review of peripheral blood by an attending hematology physician is available on request. To compare the times of clinical diagnosis and laboratory diagnosis, all charts were reviewed for the date on which the diagnostic criteria for TMA were met. Clinical management decisions were at the discretion of the treating physician.

Demographic, clinical and outcome data were extracted from the medical record. The glomerular filtration rate (GFR) was either measured (^{m}) by nuclear medicine or estimated (^{e}) by the bedside Schwartz equation, with units of mL/min/1.73 m^2. Hematologic response to eculizumab was defined as transfusion independence and resolution of schistocytes. Renal response to therapy was defined as improvement in the urine protein-to-creatinine (UPC)

ratio to ≤2 mg/mg, that is, resolution of nephrotic range proteinuria. All UPC tests were spot tests. In addition, time to hypertension control on 2 or fewer antihypertensive medications was captured. Neurologic response was defined as return to baseline mental status and cognitive ability. CH50 level was considered elevated if above the institutional reference range (60 to 144 CAE units). Soluble C5b-9 (sC5b-9) levels were considered elevated if above the reference range of ≤244 ng/mL. Acute kidney injury was defined as a doubling of the baseline serum creatinine level. Chronic kidney disease (CKD) was staged by glomerular filtration rate.

Descriptive statistics were used to summarize patient characteristics. Continuous measures were recorded as median and range; categorical measures, as frequency and proportion. Overall survival (OS) was measured from the date of transplantation to death, or to last follow-up if censored. OS point estimates were estimated using the Kaplan-Meier method. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Over the study period, a total of 318 aHCTs were performed in 243 patients. Malignant indications for transplantation included neuroblastoma (n = 118), lymphoma (n = 51), medul- loblastoma (n = 31), other central nervous tumors (n = 18), and other tumors (n = 8). In addition, 17 patients received autologous gene therapy for childhood adrenoleukodystrophy (n = 11), Wiskott-Aldrich syndrome (n = 4), chronic granulomatous disease (n = 1), or X-linked severe combined immunodeficiency (n=1).

TA-TMA was diagnosed in 9 of the 243 patients (3.7%) (Table 1), including 3 females. The median age at the time of aHCT was 3 years 5 months (range, 18 months to 25 years). TMA was diagnosed at a median of 35 days (range, 8 to 106 days) after stem cell infusion. On a retrospective chart review using the same criteria used by the provider, patients met the criteria a median of 5 days (range, 0 to 38 days) before the provider diagnosis.

Seven patients (78%) diagnosed with TA-TMA had high-risk neuroblastoma. All patients with neuroblastoma developed TA-TMA after conditioning with carboplatin, etoposide, and melphalan, including 5 after a second tandem transplantation with the first aHCT conditioned with thiotepa and etoposide, 1 after metaiodobenzylguanidine (MIBG) therapy and subsequent autologous cell rescue, and 1 after a single aHCT. Among the patients with neuroblastoma, 3 developed TA-TMA before receiving further post-aHCT neuroblastoma-directed therapy (patients 1, 2, and 3), 1 developed TA-TMA during radiation therapy (patient 8), and 3 developed TA-TMA after radiation while receiving antibody therapy (patients 4, 5, and 7). The overall prevalence of TA-TMA after aHCT in patients with neuroblastoma was 6% (7 of 118). In addition, TMA developed in 1 young adult who underwent aHCT for Hodgkin lymphoma and in 1 child who underwent aHCT for medulloblastoma. The prevalence of TA-TMA after aHCT was 2.3% (1 of 44) in patients with Hodgkin lymphoma and 3.2% (1 of 31) in those with medulloblastoma. Two patients were diagnosed with TA-TMA before 2010 using the IWG criteria, and the remainder were diagnosed using Cho et al criteria. No patient underwent biopsy or autopsy to confirm TMA diagnosis.

The kidney was the most commonly affected organ, with acute kidney injury occurring in 8 of 9 patients (89%). For the entire cohort, during the acute TMA episode, the GFR decreased from a pre-HCT median of 101 mL/min/1.73 m^2 (range 74 to 218 mL/min/1.73 m^2) to 30 mL/min/1.73 m^2 (range, >10 to 80 mL/min/1.73 m^2), a median reduction of 86% (range, 7% to 204%). Two patients required renal replacement therapy for acute renal failure. Eight patients (89%) had persistent blood pressure values >99th percentile, and 5 of 9 (56%) presented with hypertensive urgency. Among the hypertensive patients, the median number of antihypertensive medications required to normalize blood pressures was 5 (range, 2 to 6). Seven of 9 patients (78%) had proteinuria in the nephrotic range (>2 mg/mg), with a median urine protein to creatinine ratio of4 mg/mg (range, 1 to 31.3 mg/mg).

Other organs were involved at presentation of TA-TMA in 5 of 9 patients (56%). Three patients had pericardial effusions, 2 with tamponade physiology that necessitated pericardiocentesis. Four patients developed acute respiratory failure necessitating mechanical ventilation, and 1 patient required a chest tube for persistent pleural effusions. One patient had severe pulmonary hemorrhage that ultimately led to death, and 1 patient had neurologic symptoms at presentation that manifested as stupor and the loss of ability to speak and ambulate. No patient had pulmonary hypertension or gastrointestinal symptoms. Eight patients (89%) required an intensive care unit level of care during their TA-TMA course.

Two of the 6 patients in whom serum complement levels were checked had abnormal results. One patient (patient 6) had an elevated SC59-b of 460 ng/mL (reference range, <244 ng/mL) and an elevated CH50 of 183 CAE (reference range, 101 to 144 CAE). Patient 3 did not have a sC59-b level collected but did have an elevated CH50 level of 174 CAE. The median CH50 level at diagnosis was 115 (range, 101 to 182) in the 6 patients in whom it was collected. Among the 4 patients who had a sC59-b level, the median value was 151.5 ng/mL (range, 100 to 460 ng/mL).

Patients Observed/Treated with Supportive Care Only

Three patients were diagnosed with TMA before 2010, when the use of eculizumab was uncommon at our center and were treated with supportive care only. Patient 8 presented with severe TMA and was managed with 6 antihypertensive medications. He achieved platelet transfusion independence by 3 months after diagnosis and RBC transfusion independence by 6 months after diagnosis. He developed stage 4 CKD and remained on 3 to 4 medications for his refractory hypertension until he died of relapsed neuroblastoma. Patient 9 developed TA-TMA after the second of 3 planned aHCTs for medulloblastoma. She was critically ill, intubated, supported with renal replacement for renal failure, developed heart failure, and experienced seizures. She achieved transfusion independence by 2 months after diagnosis of TA-TMA, and her UPC dropped below the nephrotic range by 10 months after diagnosis, although she continued to require 4 hypertensive medications for blood pressure control. Stage 4 CKD prevented her from undergoing the third planned aHCT. She died from relapsed medulloblastoma at 2 years after discontinuation of therapy.

The final untreated patient (patient 7) had a more indolent course. His TA-TMA developed at the end of radiation therapy for neuroblastoma. He was treated supportively with 2

antihypertensive medications. After 3 weeks, he was transfusionindependent. His UPC ratio dropped from 24 mg/mg to <2 mg/mg in 4 weeks. He exhibited some recovery of his renal function with a new baseline GFR of 70 mL/min/1.73 m^2 and was able to complete the remainder ofhis neuroblastoma antibody therapy. At the time of this report, he was alive with no evidence of recurrent neuroblastoma at 3 years off therapy, although he has stage 2 CKD.

Patients Treated with Eculizumab

Six patients (67%) received eculizumab a median of 0 days (range, 0 to 11 days) after TA-TMA diagnosis by a provider and a median of 18 days (range, 0 to 58 days) after meeting the criteria for TA-TMA based on a retrospective chart review. The drug was dosed per weight as recommended in the package insert and was administered as needed to maintain a CH50 of 0 to 3 CAE (Table 2). CH50 levels ranged from 0 to 5 CAE during induction and from 0 to 8 CAE in maintenance. Two patients (patients 2 and 6) died of multiorgan failure during induction therapy without hematologic or renal response. Patient 2 died in the setting of recurrent secondary hemophagocytic lymphohistiocytosis and candidemia, both of which were present before aHCT. Patient 6 died of pulmonary hemorrhage, presumably secondary to TA-TMA.

Of the survivors (n=4), all had a hematologic response, with a median response time of 6.5 weeks (range, 4 to 9 weeks), and all had a renal response with a decrease in UPC ratio below nephrotic range at a median of 21 weeks (range, 13 to 25 weeks). Patient 1 had a hematologic and renal response and survived but never recovered neurologic function, and developed a refractory seizure disorder. Patient 3 had a hematologic and renal response to eculizumab, and treatment was stopped after 4 weekly doses of induction when his CH50 level was appropriately low at 0 CAE. Two months later, shortly after completing radiation therapy, he had recrudescence of TA-TMA, as evidenced by hemolysis, acute kidney injury, and recurrent hypertension. Eculizumab was restarted, and after his second induction, he had a hematologic response in 9 weeks and a renal response in 13 weeks. His associated stage 3 CKD delayed neuroblastoma-directed antibody therapy and necessitated renal dosing/ exclusion of some medications. He remains on 4 hypertensive agents and indefinite maintenance dosing of eculizumab per renal provider preference.

Two patients had both hematologic and renal responses (patients 4 and 5) but received prolonged eculizumab. Patient 4 had severe, poorly controlled hypertension on 5 hypertensive medications and was continued on eculizumab because it was thought to help control his hypertension. After 20 months of therapy, his GFR recovered and hypertension improved, so eculizumab was stopped. At the time of this report, he has been off eculizumab for 6 months and is stable on 2 antihypertensive medications. Patient 5 had kidney disease before aHCT related to tumor compression of her ureter, although she did not have hypertension or proteinuria before being diagnosed with TMA. After treatment with eculizumab, she had persistent, severe kidney disease and hypertension and developed heart failure and lung disease of unclear etiology. Although currently her TA-TMA appears to be quiescent, she still receives maintenance therapy 22 months after her TMA diagnosis owing

to her provider's concern that recrudescence of disease could be life- threatening given her multiorgan dysfunction.

The median duration of follow-up after diagnosis of TA-TMA was 2.5 years (range, 9 months to 4 years). OS was 78% ± 14% at 1 year post-transplantation and 65% ± 35% at 2 years posttransplantation. However, no survivor achieved normalization of function in all involved organs, even those treated with eculizumab. All eculizumabtreated survivors experienced at least 1 long-term complication: stage 3 CKD in 2 patients and persistent hypertension, congestive heart failure, and developmental delay and seizure disorder in 1 patient each.

DISCUSSION

We report 9 patients who developed TA-TMA after aHCT. TA-TMA occurred most frequently in patients with neuroblastoma (78%). Others have postulated that children with neuroblastoma have unique risk factors for the development of TA-TMA, including repetitive platinum based-chemotherapy and radiation to the kidney [1]. Most previously reported patients with neuroblastoma and patients in our cohort who develop TA-TMA had undergone tandem aHCT, so perhaps this is also a risk factor. Interestingly, patients with medulloblastoma also receive multiple cycles of induction with platinum-based therapy and can undergo up to 3 planned aHCTs for treatment. However, in our cohort, TA-TMA occurred only infrequently in these patients (prevalence of 3.2%). Thus, we postulate that children with neuroblastoma may have additional unique risk factors related to their disease, including endothelial exposure to high levels of catecholamine in combination with their therapy, including radiation and antibody therapy [1,2]. To our knowledge, these are the first reported cases of TA-TMA in children after aHCT for other indications, including Hodgkin lymphoma and medulloblastoma. These cases demonstrate that although TA-TMA may be a rare complication of aHCT, given the poor outcomes, a high index of suspicion should be maintained in all patients regardless of the underlying disease.

The prevalence of TA-TMA in children with neuroblastoma in our cohort was 6% (7 of 118), substantially lower than other reports of 30% [1,2]. This discordance may be multifactorial. Patients were identified using billing codes and departmental records; it is possible that this methodology missed some patients, which is a weakness of our study. The characteristics of TA-TMA are common to many post-HCT complications, and thus TMA may be underdiagnosed, which also could contribute to the different prevalence in this cohort. In addition, this long study period included a time when TA-TMA was less well recognized and when less-inclusive diagnostic criteria for TA-TMA (ie, the IWG criteria) were standard.

This patient cohort comprised patients with severe TA-TMA who were very ill. Historically, high-risk patients not receiving TA-TMA-directed therapy have had poor outcomes with a 1-year OS of approximately 20% [13]. None of the 3 patients who received only supportive therapy died of TA-TMA-related complications, although 2 had stage 3 CKD. At 2 years, only 1 patient was alive, and all mortality was ascribed to relapse. With only 3 patients in this group, no conclusions can be drawn about the discrepancies in these outcomes.

Multiple studies have evaluated the efficacy of eculizumab for treating TA-TMA in children. In a neuroblastoma cohort, all 6 patients treated with eculizumab recovered from multiorgan injury, allowing subsequent radiation and antibody therapy, and only 1 of the 6 had CKD [2]. In this cohort of 6 eculizumabtreated survivors, 4 survived, and all survivors had chronic end-organ disease. We also describe the first case to our knowledge of TMA recurrence after stopping eculizumab. Although this patient initially had hematologic and renal responses, he did not receive the recommended maintenance doses, so it is impossible to know if he was inadequately treated or if his disease would have recurred regardless. A sCD9-b level was not obtained at TA-TMA diagnosis, but he had evidence of appropriate complement blockade with a CH50 level of <3 CAE after therapy. We also report 2 children who were treated with eculizumab for a prolonged period, 1 for blood pressure control and 1 because of provider preference. Continuing eculizumab indefinitely is not without risk and likely is not appropriate for most children with TA-TMA; however, we suggest that these cases highlight the discomfort that providers have with stopping eculizumab in children in whom recurrence of TA-TMA could be renally catastrophic and life-threatening [5,6].

It has been hypothesized that the timing of eculizumab therapy is critical, with earlier treatment resulting in better outcomes [12,13]. To determine whether a delay in diagnosis contributed to outcomes in this cohort, the day on which patients met the criteria for TA-TMA was retrospectively assessed. Two eculizumab-treated patients had no delay in diagnosis. The remaining 4 met the criteria for TMA before a provider diagnosis, with a wide range of 5 to 58 days. Whether, and if so, how these delays affect outcomes are unclear. These findings again highlight the critical need for a high degree of suspicion for TA-TMA after HCT.

Although numerous studies have reported the OS of patients with TA-TMA, there are very few studies of late organ effects in treated survivors. In a retrospective report of 15 children with TA-TMA treated with therapeutic plasma exchange, the cumulative incidence of severe CKD was 33% [17]. The extensive end-organ damage seen in this cohort after treatment is more consistent with outcomes reported in an adult cohort of 10 patients treated with eculizumab for TA-TMA after allogeneic HCT. Overall survival was 60%, but only 1 patient had full organ recovery [18]. More studies are needed to examine the impact of treatment on late organ function in survivors, particularly in aHCT.

Variations in genes controlling complement activation are suspected to impact the risk of developing of TA-TMA and also may affect disease severity and response to therapy [10]. Abnormalities of the complement system as measured by sC5b-9 have been reported in up 72% of children with TA-TMA [7].An interesting difference in this cohort of severe TA-TMA is that 4 of 6 patients had no evidence of abnormal serum complement activity. At our institution, sC5b-9 is a send-out test; given the heat sensitivity and instability of complement samples, perhaps these values reflect technical errors and not true values [19]. However, in the 2 studies reporting complement gene variations in TA-TMA, concurrent serum sC5b-9 levels were not reported [2,11]. Children with aHUS, another complement-driven disease, have elevated sC5b-9 levels in only 50% of patients, even those with identified mutations in complement genes. Perhaps like aHUS, despite the role of complement in disease, serum sC5b-9 levels are not abnormal in all patients with TA-TMA. This could explain why

patients with normal sC5b-9 levels respond to eculizumab. This is again consistent with aHUS, in which responses to eculizumab have been reported in children without normal serum complement levels [20]. Complement genotyping may be helpful in patients with TMA and additional study is needed to determine whether elevated sC5b-9 levels predict response to eculizumab.

In summary, these cases widen the spectrum of disease previously reported by describing TA-TMA after aHCT in children with diagnoses other than neuroblastoma, severe TA-TMA in children with normal serum complement studies who responded to eculizumab, and late organ dysfunction in survivors regardless of treatment. We suggest that these cases highlight the need for prospective, multicenter studies evaluating risk factors for TA-TMA after aHCT, predicting the severity of disease, and understanding the impact of treatment on survival and long-term organ function.

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Table 1

Characteristics and Outcomes of Children Who Developed TA-TMA after aHCT

	Patients Treated with Eculizumab						Patients Not Treated		
Characteristic/Outcome	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Disease	NB	NB	NB	NB	NB	HL	NB	NB	MB
Therapy before HCT	6 cycle induction	6 cycle induction	5 cycle induction	5 cycle induction	7 cycle induction	ABVD	6 cycle induction	5 cycle induction	3 cycle induction
Age at HCT	3 yr 5 mo	8 y 11 mo	2 yr 7 mo	3 y 5 mo	7 yr	25 yr	18 mo	2 yr 3 mo	5 yr 8 mo
Sex	Male	Male	Male	Male	Female	Female	Male	Male	Female
Number of HCTs	2	2	2	2	2	1	1	2	2
Comorbidities	N/A	HLH, candidemia	N/A	N/A	Kidney disease	DD, MD	Kidney disease	N/A	N/A
Conditioning	CEM	CEM	CEM	CEM	CEM	BEAM	CEM	CEM	Cy/thiotepa
Day TA-TMA diagnosed by provider *	35	12	9	93	96	19	106	43	8
Day met criteria for TA-TMA retrospectively *	35	7	9	35	85	10	106	10	8
Potential TA-TMA trigger	–	Infection (*Candida*)		Antibody therapy	Antibody therapy	–	Antibody therapy	Radiation	–
Renal presentation									
Spot UPC, mg/mg	3.17	1	2.3	4	20.4	1.05	24.1	25.3	31.3
Hypertension	Yes	No	Yes	Yes	Yes	yes	Yes	Yes	Yes
Maximum number of anthypertensive medications	2	–	4	5	5	3	2	6	4
Other organ presentation									
Cardiac	Pericardial effusion	Hypotension	–	–	–	Pericardial effusion	–	Pericardial effusion	CHF
Pulmonary	ARF	ARF	–	–	–	ARF	–	–	ARF
Neurologic	AMS	–	–	–	–	–	–	–	Seizures
Other	Pleural effusion	–	HTN urgency	HTN urgency	HTN urgency	Pulmonary hemorrhage	HTN urgency	HTN urgency	HTN urgency
Interventions									
Intubation	Yes	Yes	No	No	No	Yes	No	No	Yes
HD	No	Yes	No	No	No	No	No	No	Yes
Other	Pericardiocentesis	–	–	–	–	–	–	Pericardiocentesis	–
Complement at diagnosis									

	Patients Treated with Eculizumab						Patients Not Treated		
Characteristic/Outcome	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
CH50 (reference range 60–144 CAE)	115	115	174	105	101	182	–	–	–
SC5b-9 (reference range ≤244 ng/mL)	–	100	–	133	170	460	–	–	–
Pre HCT GFR	101[m]	93[m]	172[m]	173[m]	96[m]	74[m]	116[m]	218[m]	134[m]
GFR nadir	<15[e]	30[e]	20[m]	80[e]	35[e]	67[e]	43[e]	14[m]	<10[e]
Post-TA-TMA GFR at baseline	76[e]	–	40[m]	132[e]	55[e]	–	70[m]	34[e]	33[m]
Alive/dead	Alive	Dead	Alive	Alive	Alive	Dead	Alive	Dead	Dead
Cause of death		MOF/HLH/ TA-TMA				Pulmonary hemorrhage		Relapse	Relapse
Time of death after HCT		D +32				D +56		1 yr 8 mo	4 yr 4 mo
Follow-up time	3 yr		9 mo	20 mo	22 mo		3.5 yr		
Long-term complications	DD, seizure disorder		Stage 3 CKD	Persistent HTN	Stage 3 CKD, CHF, lung disease		Stage 2 CKD		

NB indicates neuroblastoma; HL, Hodgkin lymphoma; MB, medulloblastoma; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; HLH, hemophagocytic lymphohistiocytosis; DD, developmental delay; MD, muscular dystrophy; CEM, carboplatin, etoposide, and melphalan; BEAM, carmustine, etoposide, cytarabine, and melphalan; Cy, cyclophosphamide; HTN, hypertension; ARF, acute respiratory failure; CHF, congestive heart failure; AMS, altered mental status; HTN, hypertensive; HD, hemodialysis; MOF, multiorgan failure.

[*] Potential trigger of relapsed TA-TMA, no clear trigger of initial presentation.

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Table 2

Treatment Courses and Responses ofPatients Treated with Eculizumab

Parameter	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Day TA-TMA treated	35	21	9	93	107	19
Day from TA-TMA diagnosis by provider	0	9	0	0	11	0
Day from TA-TMA diagnosed retrospectively	0	14	0	58	22	9
Induction therapy	Weekly × 4	Weekly × 2	Weekly × 4; second induction after relapse, weekly × 4	Weekly × 4	Weekly × 4	Weekly × 5
Range of CH50 levels during induction (CAE)	0–2	0–3	0–5	0–1	0–3	0–4
Maintenance therapy			After second induction			
Frequency of dose	Every other week	–	Every other week *	Every other week	Every other week *	–
Number of doses	3	–	4	54	50 *	–
Total time treated	10 wk	2 wk	5 mo *	20 mo	22 mo *	5 wk
Range of CH50 levels in maintenance	0–4	0–3	0–1	0–3	0–8	–
Hematologic response time, wk	9	NR	9 †	4	4	NR
Renal response time, wk	18	–	13 †	24	25	NR
Time when HTN controlled on ≤2 medications, wk	7	–	–	48	32	NR
Neurologic response	NR	N/A	N/A	N/A	N/A	N/A

Eculizumab response defined as hematologic- transfusion independence and resolution of schistocytes. Renal responses defined as a spot UPC ratio ≤2 g/dL NRindicates nonresponder; N/A, not applicable.

*Continues on eculizumab as oflast follow-up.

†Response time from second induction after TA-TMA relapse.

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