Local territory-wide experience on challenges in management of transplant-associated thrombotic microangiopathy in Hong Kong

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Abstract

Transplant-associated thrombotic microangiopathy (TA-TMA) is an under-recognized yet potentially devastating complication of hematopoietic stem cell transplantation which had increased awareness in recent years. This report summarizes territory-wide experience of paediatric TA-TMA in the Hong Kong Children's Hospital from 1 April 2019 to 31 March 2021. Total six patients were identified among 73 transplants performed. Median duration of onset was 2.5 months post-HSCT. Three patients died while all 3 survivors suffered from stage 2 to 5 chronic kidney disease despite administration of eculizumab. To conclude, recognition and diagnosis of TA-TMA is challenging. Clinical utility of complement blockage with eculizumab is limited.

Brief report

Local territory-wide experience on challenges in management of transplant-associated thrombotic microangiopathy in Hong Kong

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Abbreviations

CKD	chronic kidney disease
CNI	calcineurin inhibitor
CSA	cyclosporine
GFR	glomerular filtration rate
GVHD	graft-versus-host disease
HKCH	Hong Kong Children's Hospital
HSCT	hematopoietic stem cell transplantation
HUS	hemolytic-uremic syndrome
LDH	lactate dehydrogenase
TA-TMA	transplant-associated thrombotic microangiopathy
TTP	thrombotic thrombocytopenic purpura

ABSTRACT

Transplant-associated thrombotic microangiopathy (TA-TMA) is an under-recognized yet potentially devastating complication of hematopoietic stem cell transplantation which had increased awareness in recent years. This report summarizes territory-wide experience of paediatric TA-TMA in the Hong Kong Children's Hospital from 1 April 2019 to 31 March 2021. Total six patients were identified among 73 transplants performed. Median duration of onset was 2.5 months post-HSCT. Three patients died while all 3 survivors suffered from stage 2 to 5 chronic kidney disease despite administration of eculizumab. To conclude, recognition and diagnosis of TA-TMA is challenging. Clinical utility of complement blockage with eculizumab is limited.

MAIN BODY TEXT

Introduction

Transplant-associated thrombotic microangiopathy (TA-TMA) is an under-recognized yet potentially devastating complication of hematopoietic stem cell transplantation (HSCT) characterized by endothelial damage, intravascular activation and platelet sequestration, accumulation of microthrombi occluding microcirculation, and red blood cells fragmentation causing non-immune microangiopathic hemolytic anemia (1). Clinical and laboratory features include the triad of hypertension, thrombocytopenia and elevation of lactate dehydrogenase (LDH); as well as schistocytosis in peripheral blood smear, thrombocytopenia, decreased haptoglobin level, and target organ damage such as renal impairment. It had increasingly been identified in recent years (2-5) in both autologous and allogeneic HSCT settings. Reported incidences of TA-TMA vary widely from

0.5% to 76% due to different diagnostic criteria, demographic characteristics, conditioning regimen, donor source, and co-morbidities (6-22). TA-TMA carries a high mortality of 30% to 90% (7, 12, 17, 20, 21, 23), depending on its severity and presence of co-morbidities. This report summarized the experience of TA-TMA in the Hong Kong Children's Hospital (HKCH), the only territory-wide paediatric transplant centre in Hong Kong since its establishment in 2019, highlighting challenges in management of TA-TMA in this locality.

Methods

All patients aged below 18 years of age who underwent HSCT in HKCH and diagnosed to have TA-TMA during the 2-year study period from 1 April 2019 to 31 March 2021 were included. Data on basic demographics, transplant details, potential risk factors for pathogenesis of TA-TMA, clinical and laboratory presentations of TA-TMA, subsequent treatment and outcomes were collected.

Results

Total 73 transplants (51 allogeneic, 22 autologous) had been performed in 63 patients during the study period. Six patients (4 males and 2 females) developed TA-TMA at a median duration of 2.5 months post-HSCT. Incidence rate was 9.52%. For the six TA-TMA patients, five underwent allogenic HSCT while one underwent autologous HSCT. Three out of six cases of TA-TMA were histologically proven. Demographics and transplant details are described in **Table 1a** . All five patients who underwent allogeneic HSCT developed various degrees of acute graft-versus-host disease (GVHD) and viral infections. Four used calcineurin inhibitor (CNI) cyclosporine (CSA) as GVHD prophylaxis which was stopped once TA-TMA was suspected. Three out of six patients developed hepatic sinusoidal obstruction syndrome with defibrotide given. Genetic predisposition had not been identified in local cohort except identification of a variant of unknown significance in THBD gene for **Case 6 (Table 1b)** . All six patients developed hypertension, proteinuria, schistocytosis with elevated LDH. Five out of six had anemia, thrombocytopenia, elevated creatinine, elevated d-dimer and low haptoglobin level **(Table 1b)** . Median six doses (range 4 to 12 doses) of eculizumab were administered to four out of six patients. Serum eculizumab level was not performed due to unavailability of the test. Three patients died (2 due to fungal infection and one due to acute-on-chronic renal failure) **(Cases 1 to 3)** and all within 3 months upon diagnosis of TA-TMA. Mortality rate was 50%. All three survivors **(Cases 4 to 6)** suffered from chronic kidney disease (CKD) and one **(Case 5)** required lifelong dialysis**(Table 1c)** .

Discussion

1. Challenges in recognizing and diagnosing TA-TMA

TA-TMA is difficult to recognize as complex clinical picture post-HSCT can mask or mimic TA-TMA, such as cytopenia due to marrow aplasia before engraftment, drug-induced hypertension and immune-mediated hemolysis. Besides, as not all features appear simultaneously and may evolve over days to weeks, high index of suspicion is crucial to pick up subtle cues of evolving TA-TMA such as persistent hypertension requiring multiple anti-hypertensives, elevated LDH, or increased transfusion requirement and platelet refractoriness. There has yet been a universally accepted diagnostic criteria for TA-TMA. Histology is the most reliable modality yet invasive and risky. Diagnostic triad of hypertension, thrombocytopenia and elevated LDH proposed by Dvorak (2) provides useful guidance in recognizing TA-TMA, though proteinuria instead of thrombocytopenia is the third universal feature in local cohort **(Table 1b)** .

2. Challenges in assessment of therapeutic efficacy

Management algorithm proposed by Jodele et al (24) stratifies high risk TA-TMA patients as indication for eculizumab use with therapeutic drug level monitoring. Clinical utility of this guideline is limited in local setting as measurement of both soluble terminal complement complex (sC5b-9) and eculizumab drug level are not readily available in local laboratories. Long turnaround time due to transportation to overseas accredited laboratories limits its use in facilitating timely clinical decision making and management. Besides, eculizumab is currently licensed only for treating atypical hemolytic-uremic syndrome (HUS) and paroxysmal nocturnal hemoglobinuria. Off-label use of eculizumab for TA-TMA costs USD$6,700 per 300mg vial, which has great

financial implication on public healthcare system. Moreover, although decline in glomerular filtration rate (GFR) and thus degree of kidney injury is better evaluated by cystatin C (by Larsson formula) instead of serum creatinine (by Schwartz formula) which is a late and insensitive parameter particularly in young patients with low muscle mass and low creatinine generation rates, cystatin C test is also not available in local setting.

3. Pathogenesis, risk factors and prevention

Three-hit hypothesis proposed by Kosala et al (25) and Dvorak et al (2) provide insights on pathogenesis of TA-TMA. For the "first hit" (initiation phase), patients either have an underlying predisposition to complement activation (e.g., racial or genetic factors) or a pre-existing endothelial injury (e.g., prior myeloablative conditioning or prolonged use of calcineurin inhibitors). Genetic predisposition had not been identified in local cohort except identification of a variant of unknown significance in THBD gene for**Case 6 (Table 1b)** . For the "second hit" (progression phase), delivery of conditioning regimen mediates further endothelial injury. Injured endothelium exposes damage-associated molecular patterns, which activates C3 to initiate alternative pathway activity in the complement system. The "third hit" refers to complement activation by drugs, GVHD, infection or antibodies. Usage of eculizumab in local cohort readily suppressed classical and alternative complement pathway (the "third hit"), normalized haematological parameters, and resolved hypertension and proteinuria, but damage to kidneys and decline in GFR are irreversible **(Table 1c)** .

Risk factors for development of TA-TMA include female sex (9, 17, 26, 27), older age (9, 16, 17, 26) , genetic variants in complement activation (28), alternative donor transplant (16, 17, 22, 26), blood group incompatibility (15, 26), intensive conditioning regimen (16, 18), particularly those containing high dose busulphan (13) or irradiation (17, 27), use of antithymocyte globulin (14), calcineurin inhibitor as GVHD prophylaxis (13), infections (20, 27), and presence of GvHD (13, 15-18, 20, 22, 26, 27, 29). Vitamin D, eicosapentaenoic acid (EPA), allopurinol, statin, and defibrotide are all potentially useful compounds in preventing TA-TMA but their efficacy and safety has yet to be elucidated.

4. Prognostic factors

Reported prognostic factors associated with poor outcome include elevated LDH (20), acute kidney injury (20), proteinuria (>30 mg/dL)(23), and raised plasma sC5b-9 at diagnosis (23). Patients with proteinuria and elevated sC5b-9 at diagnosis had 84% mortality while all patients without proteinuria or elevated sC5b-9 survived. Pulmonary hypertension is another poor prognostic factor with 80% mortality (30). Elevated right ventricular pressure at day +7 post-transplant was significantly associated with subsequent development of TA-TMA (25, 31).

Conclusion

In conclusion, recognition and diagnosis of TA-TMA is challenging. Clinical utility of complement blockage with eculizumab is limited in terms of therapeutic efficacy, response monitoring and financial implications. Further prospective research studies on alternative agents are warranted to improve treatment and outcomes of TA-TMA.

Disclosure

All authors have disclosed no conflicts of interest.

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Legend

Table 1a Transplant details for local territory-wide cohort for transplant-associated thrombotic microangiopathy (TA-TMA)

Table 1b Clinical and laboratory presentations of local territory-wide cohort for transplant-associated thrombotic microangiopathy (TA-TMA)

Table 1c Treatment and outcomes of local territory-wide cohort for transplant-associated thrombotic microangiopathy (TA-TMA)

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