Indian J Hematol Blood Transfus (July-Sept 2018) 34(3):469–473
https://doi.org/10.1007/s12288-017-0904-y

SHORT COMMUNICATION

Successful Treatment of Transplant Associated Thrombotic Microangiopathy (TA-TMA) with Low Dose Defibrotide

Santhosh Kumar Devadas[1] · Manoj Toshniwal[1] · Bhausaheb Bagal[1] · Navin Khattry[1,2]

Received: 20 August 2017 / Accepted: 20 November 2017 / Published online: 23 November 2017

Abstract Transplant associated microangiopathy (TA-TMA) is a potentially serious complication of stem cell transplantation. Though stopping calcineurin/mTOR inhibitor is the first step in managing TA-TMA, this is not always adequate. The pathophysiology of TA-TMA is different from microangiopathy seen in other settings. Many drugs have been used in TA-TMA with modest responses. Defibrotide has been explored in TA-TMA in the past with good results. However, its availability is erratic and cost of therapy very high. Hence its routine use in low middle income country (LMIC) is financially demanding. We report the use of low dose defibrotide safely and successfully in this case series. This is pertinent more to LMIC's and warrants prospective evaluation.

Keywords Defibrotide · Allogeneic · Transplant · Microangiopathy

Introduction

Transplant Associated Thrombotic Microangiopathy (TA-TMA) is a life-threatening complication after hematopoietic stem cell transplantation (HSCT). It remains a difficult problem faced by transplant physicians' world over, not only due to associated mortality and morbidity but also due to diagnostic uncertainties and lack of effective therapeutic options [1]. Incidence of TA-TMA is between 10 and 35% depending on the diagnostic criteria used and various risk factors [2, 3]. Estimated mortality in patients who develop TA-TMA is 60–90% with a high prevalence of chronic kidney disease many of the survivors [4, 5]. Therapy options for TA-TMA not responding to stoppage of CNI/mTOR inhibitors is limited. We report three cases of treatment of TA-TMA with low dose defibrotide.

Materials and Methods

We retrospectively reviewed the case files of three patients with TA-TMA treated with low dose defibrotide (i.e. < 10 mg/kg/day) and their outcomes. The salient clinical features are enumerated in Table 1. TA-TMA was diagnosed based on the International Working Group criteria [6].

Results

Patient 1

A 24-year-old male with AML in second remission, underwent haplo-identical HSCT from his father. Conditioning regimen used was fludarabine (30 mg/m^2/day for 5 days) and busulfan (3.2 mg/kg/day I.V. for 3 days) and post-transplant cyclophosphamide (50 mg/kg/day on day $+3$ and $+4$) followed by cyclosporine (CSA) and mycophenolate mofetil (MMF) as GVHD prophylaxis was used. On day $+25$ he developed thrombocytopenia, rise in serum LDH, fall in hemoglobin level and peripheral smear showed 8–10 schistocytes/hpf. Cyclosporine was stopped.

✉ Navin Khattry
nkhattry@gmail.com

[1] Bone Marrow Transplant Unit, ACTREC, Tata Memorial Centre, Sector 22, Kharghar, Navi-Mumbai, India

[2] Department of Medical Oncology, Room No. 247, Paymaster Shodhika, ACTREC, Tata Memorial Centre, Sector 22, Kharghar, Navi-Mumbai 410210, India

Table 1 Salient clinical features of the three patients with TA-TMA

Pt no	Age (yrs)	Sex	Diagnosis	Transplant	GVHD site and grade	Symptoms	Serum LDH baseline (U/L)	Serum LDH max (U/L)	Serum creatinine baseline (mg/dl)	Serum creatinine Max (mg/dl)	DF dose mg/kg/day	Duration of DF (days)	Outcome	Cause of death
1	24	M	AML-CR2	Haplo	Nil	Altered sensorium Acute renal failure	405	2332	0.6	1.18	7.5	7	Alive	NA
2	29	M	CML-AP	MSD	Gut- II	Altered sensorium Seizures	143	730	0.81	0.97	4.0	9	Alive	NA
3	49	M	ALL-CR1	MUD	Gut-III	Diarrhea Ascites Altered sensorium Acute renal failure	178	775	0.68	1.7	7.5	19	Dead	Sepsis

MSD matched sibling donor, *MUD* matched unrelated donor

He had elevated serum creatinine (baseline 0.6 mg/dl increased to a maximum of 1.18 mg/dl) by day + 27 followed by altered sensorium which waxed and waned. MRI brain and CSF examination were normal. He was started on Defibrotide at 200 mg every 8 h (7.5 mg/kg/day) on day + 31. He showed a dramatic improvement in neurologic state and altered sensorium in the next 3 days. The serum LDH and serum creatinine showed a decreasing trend. Defibrotide was stopped on day + 37 due to further non-availability. He did not have recurrence of the above symptoms. He remains well after more than 36 months of transplant.

Patient 2

A 29-year-old male with chronic myeloid leukemia-Accelerated Phase (CML-AP), underwent matched related sibling transplant from his sister. Conditioning regimen used was fludarabine (30 mg/m2/day for 5 days) and melphalan (140 mg/m^2). Cyclosporine and methotrexate (MTX) were used as GVHD prophylaxis. He presented on day + 47 with gut GVHD. He was started on Inj methylprednisolone at 2 mg/kg/day. Inj etanercept 25 mg subcutaneous every 72 h was added on day + 64 for steroid refractory GVHD. As gut GVHD started showing signs of resolution, steroid tapering was initiated. On day + 81 he developed episodes of altered sensorium and agitated behavior. MRI brain and CSF analysis were normal. Peripheral smear showed 8–10 schistocytes/hpf. Serum LDH was elevated. Serum creatinine levels remained normal. With a diagnosis of TA-TMA, cyclosporine was stopped on day +83. However, the episodes of irrational behavior persisted. He was started on Inj defibrotide at a dose of 200 mg IV 12 hourly (4 mg/kg/day) from day + 111 till day + 119. The irrational behavior and agitation gradually subsided. Percentage of schistocytes in the peripheral smear reduced and serum LDH improved. He is presently well, is off all immune-suppression with no evidence of any chronic kidney damage more than 2 years' post-transplant.

Patient 3

A 49-year-old male with Pro-B ALL who underwent matched unrelated donor transplant in 1st remission was admitted with increased frequency of stools and bloody diarrhea on day + 90 post-transplant. With suspected gut GVHD, he was started on Inj methylprednisolone at 2 mg/kg/day on day + 96 since he did not respond to antibiotics. Though there was clinical improvement after starting steroid, on day + 102 he developed rising serum creatinine (up to 1.7 mg/dl) and hematuria. His peripheral smear revealed 5–6 schistocytes per high power field, serum LDH was elevated and his platelet and packed red cell requirement gradually increased. He also developed altered sensorium. Hence cyclosporine was stopped on day + 102. He was started on defibrotide at 200 mg every 8 hourly (7.5 mg/kg/day) from day + 105 in view of suspected TA-TMA. Gradually his neurologic state and renal functions improved. The serum LDH and number of schistocytes in the peripheral smear reduced. Defibrotide was discontinued on day + 118 in view of increased bleeding tendency. His TA-TMA improved but he finally expired on day + 162 of Klebsiella sepsis.

Discussion

The important risk factors for TA-TMA are older age, myeloablative conditioning, unrelated donor, HLA mismatch, exposure to calcineurin inhibitors (CNIs)/mTOR inhibitors, graft versus host disease (GVHD) and infections [7].

It is known that pathophysiology of TA-TMA is different from other well defined types of TMA syndromes like shiga toxin induced TMA, TMA due to deficiency of ADAMTS13 enzyme or due to mutations in proteins of the complement pathway [3, 8]. Increasing evidence suggests that TA-TMA is a multifactorial disorder distinct from thrombotic thrombocytopenic purpura (TTP) and the endothelial damage represents the final common pathway of injury [9]. TA-TMA responds poorly to conventional treatment for TTP, including plasma exchange, but newer agents known to modify endothelial responses to injury such as daclizumab, statins, prostacyclin analogues, endothelin- receptor antagonists and free radical scavengers may lead to improved outcomes for patients affected by this disorder [1, 4, 5]. Rituximab has been tried in TA-TMA, however its use does not have a strong pathogenic basis and also may be associated with flare of occult infection in an already immunocompromised patient [2, 10, 11]. Recently eculizumab which is a monoclonal antibody targeting complement factor C5a has shown good results in patients suffering from TA-TMA due to activation of complement [2]. But eculizumab is very expensive with very limited available data [11].

At the present there is no consensus on what constitutes appropriate therapy for patients with TA-TMA. Stopping of calcineurin inhibitors/mTOR inhibitors is always the first step in management of TA-TMA [3]. By analogy with the treatment of classical TTP, many centres use therapeutic plasma exchange (TPE) in the therapy of TA-TMA although it is difficult to render it in sick patients and there are no large-scale clinical trials to support its use in this disorder. TPE may correct the hematologic abnormalities associated with TA-TMA but does not improve survival

[12]. Results of retrospective studies studying each modality or drug is highly variable because the outcomes also depend on whether a treatment was started early or late into TA-TMA [3].

Defibrotide (DF) is a polydeoxyribonucleotide with novel antithrombotic properties known to cause vasodilatation, reduction in cytokine release by the vascular endothelium, increase vascular integrity and reduce thrombosis in the microvasculature leading to better organ perfusion [13]. It has shown activity in many diseases which are caused by endothelial activation and inflammation like veno-occlusive disease (VOD), antiphospholipid antibody (APLA) syndrome, vasculitis and TTP [13]. Most of the studies used defibrotide at doses between 20 and 40 mg/kg/day for a planned minimum course of 14 days. We have successfully used low dose defibrotide in VOD [14]. Though transplant literature alludes to use of defibrotide in TA-TMA, with variable success, it is not widely used by transplant physicians' for this indication mainly because of non-availability and prohibitive cost [4, 5, 11, 15, 16]. Defibrotide is probably the easiest drug to administer among the drugs that are found to be useful in this difficult to treat complication of HSCT mainly because of its minimal side effects as compared to its benefits [17]. The reported side effects of defibrotide include mild allergic reactions, gastrointestinal side effects like nausea, diarrhea etc. Rarely infusion related hypotension has been reported. Anticoagulant effects leading to increased risk of bleeding, though described is very rare. However, it is best avoided when an anticoagulant like heparin is being used in the patient [18]. In a large study by Uderzo et al. consisting of 539 patients undergoing HSCT, 64 patients developed TA-TMA, and use of defibrotide improved the outcomes on univariate analysis, however this was not statistically significant on multivariate analysis [7].

When costs of therapy are compared with eculizumab, which is another drug used in TA-TMA there is a vast difference in the prizing. Though both eculizumab and defibrotide are not available in the Indian market, they can be imported. The cost of one day therapy for low dose defibrotide (7.5 mg/kg/day) in an adult weighing 60 kg is about 1000 US dollars. The cost of Eculizumab (900 mg weekly) is much higher at about 21,000 US dollars [19]. Comparatively the cost of eculizumab is five times that of defibrotide.

All three patients who received low doses of defibrotide (i.e. < 10 mg/kg/day) for TA-TMA responded to it. While one patient eventually died of sepsis, the other two patients are well more than two-year post HSCT. In conclusion, administration of low-dose Defibrotide is an effective and well-tolerated treatment option for TA-TMA. Defibrotide seems to be an excellent drug in the management of TA-TMA because of its efficacy as a single agent, its safety and ease of administration in a sick patient. The drawback is its erratic availability and its cost. This drug should be further prospectively evaluated in a large cohort of patients with suspected TA-TMA.

Compliance with Ethical Standards

Conflict of interest The authors declare no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

References

1. Fontana S, Kremer Hovinga JA, Lämmle B, Mansouri Taleghani B (2006) Treatment of thrombotic thrombocytopenic purpura. Vox Sang 90(4):245–254
2. Jodele S, Laskin BL, Dandoy CE, Myers KC, El-Bietar J, Davies SM et al (2014) A new paradigm: diagnosis and management of HSCT-associated thrombotic microangiopathy as multi-system endothelial injury. Blood Rev 29(3):191–204
3. Laskin BL, Goebel J, Davies SM, Jodele S (2011) Small vessels, big trouble in the kidneys and beyond: hematopoietic stem cell transplantation—associated thrombotic microangiopathy. Blood 118(6):1452–1462
4. Choi CM, Schmaier AH, Snell MR, Lazarus HM (2009) Thrombotic microangiopathy in haematopoietic stem cell transplantation: diagnosis and treatment. Drugs 69(2):183–198
5. Batts ED, Lazarus HM (2007) Diagnosis and treatment of transplantation-associated thrombotic microangiopathy: real progress or are we still waiting? Bone Marrow Transplant 40(8):709–719
6. Ruutu T, Barosi G, Benjamin RJ, Clark RE, George JN, Gratwohl A et al (2007) Diagnostic criteria for hematopoietic stem cell transplant-associated microangiopathy: results of a consensus process by an International Working Group. Haematologica 92(1):95–100
7. Uderzo C, Bonanomi S, Busca A, Renoldi M, Ferrari P, Iacobelli M et al (2006) Risk factors and severe outcome in thrombotic microangiopathy after allogeneic hematopoietic stem cell transplantation. Transplantation 82(5):638–644
8. George JN, Nester CM (2014) Syndromes of thrombotic microangiopathy. N Engl J Med 371(7):654–666
9. Cooke KR, Jannin A, Ho V (2008) The contribution of endothelial activation and injury to end-organ toxicity following allogeneic hematopoietic stem cell transplantation. Biol Blood Marrow Transplant 14((1 Suppl 1)):23–32
10. Gea-Banacloche JC (2010) Rituximab-associated infections. Semin Hematol 47(2):187–198
11. Kim SS, Patel M, Yum K, Keyzner A (2015) Hematopoietic stem cell transplant-associated thrombotic microangiopathy: review of pharmacologic treatment options. Transfusion 55(2):452–458
12. Hahn T, Alam AR, Lawrence D, Ford L, Baer MR, Bambach B et al (2004) Thrombotic microangiopathy after allogeneic blood and marrow transplantation is associated with dose-intensive myeloablative conditioning regimens, unrelated donor, and

methylprednisolone T-cell depletion. Transplantation 78(10):1515–1522
13. Pescador R, Capuzzi L, Mantovani M, Fulgenzi A, Ferrero ME (2013) Defibrotide: properties and clinical use of an old/new drug. Vascul Pharmacol 59(1–2):1–10
14. Bagal B, Chandrasekharan A, Chougle A, Khattry N (2016) Low, fixed dose defibrotide in management of hepatic veno-occlusive disease post stem cell transplantation. Hematol Oncol Stem Cell Ther. https://doi.org/10.1016/j.hemonc.2017.02.005
15. Corti P, Uderzo C, Tagliabue A, Della Volpe A, Annaloro C, Tagliaferri E et al (2002) Defibrotide as a promising treatment for thrombotic thrombocytopenic purpura in patients undergoing bone marrow transplantation. Bone Marrow Transplant 29(6):542–543
16. Uderzo C, Fumagalli M, De Lorenzo P, Busca A, Vassallo E, Bonanomi S et al (2000) Impact of thrombotic thrombocytopenic purpura on leukemic children undergoing bone marrow transplantation. Bone Marrow Transplant 26(9):1005–1009
17. Richardson PG, Murakami C, Jin Z, Warren D, Momtaz P, Hoppensteadt D et al (2002) Multi-institutional use of defibrotide in 88 patients after stem cell transplantation with severe veno-occlusive disease and multisystem organ failure: response without significant toxicity in a high-risk population and factors predictive of outcome. Blood 100(13):4337–4343
18. Palmer KJ, Goa KL (1993) Defibrotide: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in vascular disorders. Drugs 45(2):259–294
19. Herper M (2010) The world's most expensive drugs. Forbes. https://www.forbes.com/2010/02/19/expensive-drugs-cost-business-healthcare-rarediseases.html#4ef154795e10