CORRESPONDENCE

Successful use of narsoplimab to treat allogeneic transplant-associated thrombotic microangiopathy while maintaining sirolimus

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TO THE EDITOR:

Hematopoietic cell transplantation-associated thrombotic microangiopathy (TA-TMA) is a unique thrombotic and inflammatory disorder that complicates the post allogeneic hematopoietic cell transplantation (alloHCT) course in up to15% of patients [1, 2], leading to a significant increase in morbidity and mortality [3]. TA-TMA has a median time-to-onset of 86 days post alloHCT [4]. Endothelial injury is the key event for TA-TMA, with subsequent endothelial cell injury propagating pro-inflammatory cytokines leading to activation of both alternative and lectin pathways of complement [5, 6]. Hemolytic anemia leading to longer-than-expected transfusion needs, thrombocytopenia and wide range of organ dysfunction characterize TA-TMA [2]. The historic lack of uniformly accepted clinical diagnostic criteria and the fact TA-TMA often coincides with other confounding complications post alloHCT that share common manifestations makes the diagnosis challenging. Efforts to build a consensus definition for TA-TMA by multiple societies have been recently published [7]. Graft-versus-host disease (GVHD) itself and the drugs typically used for prophylaxis such as calcineurin inhibitors (CNI) or mammalian target of rapamycin (mTOR) inhibitors, are often implicated in potentiating TA-TMA and complicating its diagnosis and management [8]. A growing body of evidence suggests that preexisting or novel endothelial dysfunction may create the necessary immune-inflammatory environment for TA-TMA, a process that can be exacerbated by GVHD [9, 10]. CNI cause endotheliopathy by their direct cytotoxic damage, elevated thrombomodulin and decreased prostacyclin, while mTOR inhibitors prevent endothelial repair and decrease VEGF production [11]. Withdrawal of CNI and/or mTOR inhibitors upon identifying TA-TMA has been commonly practiced as a primary intervention [12]. However, since TA-TMA can occur early in post alloHCT and/or with concomitant active GVHD, this approach can be challenging.

The use of anti-C5 monoclonal antibody eculizumab has shown promising activity in pediatric patients with TA-TMA, resulting in 66% overall survival (OS) at 1 year (compared to 16.7% in control) [13]. In adult patients with TA-TMA, small retrospective studies have reported hematological responses with eculizumab in most patients, however, with limited OS benefit, with only one third of patients alive at 30 weeks post TA-TMA diagnosis [14]. Narsoplimab (Omeros Corporation, Seattle, WA) is a novel, fully human immunoglobulin G4 monoclonal antibody that inhibits mannan-binding lectin-associated serine protease-2 (MASP2), the effector enzyme of the lectin pathway of complement. A recent phase II study evaluated the efficacy of narsoplimab prospectively in 28 patients with high-risk TA-TMA showed promising results with 61% response rate (defined as improvement in both TA-TMA markers and organ dysfunction) and 68% OS at 100 days from the date of TA-TMA diagnosis [15]. Herein, we report for the first time, a patient with high-risk TA-TMA successfully treated with narsoplimab while maintaining GVHD prophylaxis/treatment.

The patient was 65-year-old man diagnosed with high risk (MIPI 7.8) stage IV *TP53*-mutated mantle cell lymphoma (MCL) with blastoid features involving bone marrow and spleen. He was initially treated with alternating 6 cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), and rituximab, dexamethasone, cytarabine, and cisplatin (R-DHAP) every 21 days. The end-of-treatment positron emission tomography (PET) scan and bone marrow assessment confirmed complete remission. Considering the growing evidence of the benefit of consolidative alloHCT for high risk *TP53*-mutated MCL [16], he underwent 11/12 DP permissive matched-unrelated donor alloHCT conditioned with fludarabine and melphalan. GVHD prophylaxis consisted of tacrolimus, post-transplant cyclophosphamide, and itacitinib [on a clinical trial NCT03320642]. He achieved neutrophils and platelet engraftment on days +17 and day +24, respectively. PET scan 3 months post alloHCT showed no evidence of MCL with concurrent bone marrow sample demonstrated full donor chimerism. He was diagnosed with stage 1 acute GVHD of the skin 82 days post alloHCT which evolved to stage 3 on day +95. He was started on topical corticosteroids with some improvement. TA-TMA features appeared on day +103 post-alloHCT. His lactate dehydrogenase (LDH) abruptly increased to 779 U/L (reference range 130-250), Haptoglobin dropped to 10 mg/dL (reference range 40–240), Hemoglobin (Hgb) decreased to 8 g/dL (reference range 12.5-16.2), and platelet declined to 47 k/mcl (reference range 160-400). His serum creatinine rose to 1.5 mg/dL (reference range 0.6–1.3). Urine analysis revealed new hematuria and proteinuria. Blood pressure became persistently elevated. Peripheral blood smear revealed prominent schistocytosis by day +108. Direct Coomb's test was negative and there was no indication of disseminated intravascular coagulation. Soluble C5b-9 level was 208 ng/mL (reference range <251 ng/mL). By day +115, his Hgb and platelet levels continued to decline, and the hemolytic markers deteriorated as shown in Fig. 1 consistent with TA-TMA as defined by recently published, harmonized, modified Jodele criteria [7]. Tacrolimus was transitioned to sirolimus on day +119 which resulted in initial stabilization of TA-TMA markers but that followed by worsening TA-TMA around 4 weeks later with blood transfusion requirements and recurrent acute kidney injury as shown in Fig. 1. At that time,

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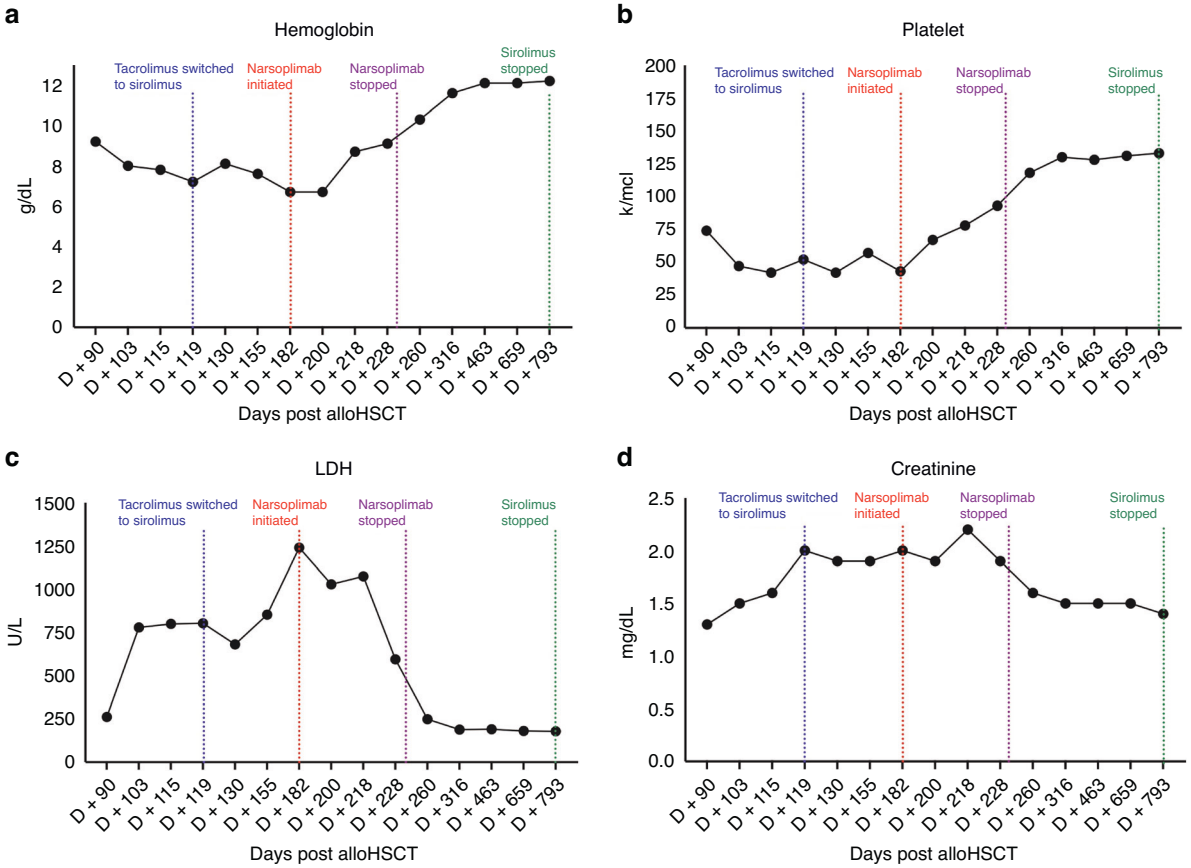

Fig. 1 Linear graphs depicting the HSCT-TMA markers' timeline upon the diagnosis, after switching tacrolimus to sirolimus, initiating narsoplimab, and the response to it. a Hemoglobin. **b** Platelets. **c** LDH. **d** Creatinine. HSCT-TMA Hematopoietic stem cell transplantation-associated thrombotic microangiopathy, LDH lactate dehydrogenase.

patient had concurrent stage 3 skin GVHD which was treated with systemic prednisone and topical corticosteroids. Skin GVHD resolved by day +175. Due to the concern of GVHD flare, a decision was made to maintain sirolimus targeting a lower therapeutic range while initiating narsoplimab for TA-TMA. Narsoplimab at a dose of 370 mg intravenously was started on day +182 post alloHCT and administered twice weekly. This Single Patient Use was approved by the Memorial Sloan Kettering Cancer Center IRB and the FDA, and the patient signed consent for treatment. We observed signs of TA-TMA treatment response to narsoplimab immediately after the first week with platelet improving and decreasing LDH. This was followed by improvement in Hgb after the second week. Schistocytes decreased to 1 per high power field before it disappeared by day +207. A response in kidney function was observed after the third week with creatinine returning to baseline accompanied by clearance of protein and blood in the urine. Narsoplimab was stopped after the thirteenth dose on day +235. Sirolimus was discontinued on day +793 after months of tapering it while controlling sporadic skin GVHD flares which eventually abated. More than 2 years after stopping narsoplimab, there is no evidence of TA-TMA and hemolytic markers were within the normal limits (Fig. 1).

Management of TA-TMA has evolved in the modern era mainly due to better understanding of the crucial role of systemic complement activation and the use of complement blockade therapy. To our knowledge, this is the first report demonstrating the feasibility of maintaining CNI/mTOR while using narsoplimab to treat high risk TA-TMA achieving full response. This report highlights a real-world scenario of the multifaceted complex approach to treat TA-TMA, which often includes controlling multiple coexisting triggering factors, most prominently, GVHD and CNI/mTOR. While CNI/mTOR withdrawal has historically been considered a first step in the management [12], it is often associated with increased risk of GVHD and was not feasible in this case since HSCT-TMA occurred early in post alloHCT course with concern of GVHD flare. Our report shows that despite the common notion that switching tacrolimus (CNI) to sirolimus (mTOR) could mitigate TA-TMA [17], multiple studies suggest sirolimus may also be implicated in TA-TMA [8] and this may not be sufficient in controlling it. Furthermore, this report shows the feasibility of discontinuing narsoplimab after controlling TA-TMA without the need for maintenance therapy often seen with eculizumab [13]. Finally, this case highlights that TA-TMA management could be individualized based on patient's condition, the spectrum of TA-TMA severity, and the presence of co-existing post alloHCT complications such as GVHD.

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DATA AVAILABILITY

Data used and/or analyzed during this submission are original and they are available from corresponding author on reasonable request.

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AUTHOR CONTRIBUTIONS

MA and MAP conceptualized and wrote the paper. MS contributed to the writing of the manuscript and provided important insight. All authors reviewed and approved the final manuscript.

COMPETING INTERESTS

MA has no conflicts of interest to disclose. MS served as a paid consultant for McKinsey & Company, Angiocrine Bioscience, Inc., and Omeros Corporation; received research funding from Angiocrine Bioscience, Inc., Omeros Corporation, and Amgen, Inc.; served on ad hoc advisory boards for Kite – A Gilead Company; and received honoraria from i3Health, Medscape, and CancerNetwork for CME-related activity. MAP reports honoraria from Adicet, Allogene, Allovir, Caribou Biosciences, Celgene, Bristol-Myers Squibb, Equilium, Exevir, ImmPACT Bio, Incyte, Karyopharm, Kite/Gilead, Merck, Miltenyi Biotec, MorphoSys, Nektar Therapeutics, Novartis, Omeros, OrcaBio, Syncopation, VectivBio AG, and Vor Biopharma. He serves on DSMBs for Cidara Therapeutics, Medigene, and Sellas Life Sciences, and the scientific advisory board of NexImmune. He has ownership interests in NexImmune, Omeros and OrcaBio. He has received institutional research support for clinical trials from Allogene, Incyte, Kite/Gilead, Miltenyi Biotec, Nektar Therapeutics, and Novartis.

ADDITIONAL INFORMATION

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