Title: *Complement-Dependent Killing Activity in Hematopoietic Stem Cell Transplant Associated Thrombotic Microangiopathy*

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Background: Hematopoietic stem cell transplant-associated thrombotic microangiopathy (HSCT-TMA) is associated with high morbidity and mortality. While complement activation is thought to drive HSCT-TMA in pediatric populations, its role in adult HSCT-TMA is less clear. The modified Ham 2.0 (mHAM 2.0) test is a functional assay that uses flow cytometry to measure complement-dependent cell killing of nucleated human cells and may help clarify the role of complement in adult HSCT-TMA.

Methods: HSCT-TMA was defined as meeting at least 3 of 4 Modified City of Hope criteria (i.e., acute kidney injury, schistocytes, elevated lactate dehydrogenase, and/or thrombocytopenia), while controls met ≤1 criterion. Cases and controls were matched on age (±5 years), sex, and baseline eGFR (±15 mL/min/1.73 m2). Samples were collected within 30 days pre-conditioning and at 7-14 days following HSCT. mHAM 2.0 was performed at both time points to assess %cell kill activity. mHAM 2.0 was performed on samples at both time points to assess %cell kill activity.

Results: Thirty-one matched case-control pairs with paired pre- and post-HSCT samples were analyzed. HSCT-TMA occurred at a median of 22 days [IQR 20-52] post-transplant. Median %cell kill was similar between HSCT-TMA cases and controls both pre- and post-HSCT (Figure 1A-D). The median change in %cell kill from pre- to post-transplant was −3.7% [IQR -15.9%-0.0%] among HSCT-TMA cases and -4.8% [IQR -7.5%-0.0%] among controls (p=0.36). In a linear mixed-effects model, there was no significant change in %cell kill from pre- to post-HSCT between cases and matched controls (p=0.99). Results were unchanged in a sensitivity analysis restricted to HSCT-TMA occurring within 30 days post-HSCT (n=18).

Conclusion: mHAM %cell kill activity did not differ between HSCT-TMA cases and matched controls before or after HSCT. Larger prospective studies, with samples obtained at the time of HSCT-TMA, are needed to clarify the role of complement in adult HSCT-TMA.

Figure 1. Complement-Dependent Killing Activity Before and After HSCT in HSCT-TMA Cases and Matched Controls.