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HIGH-RESOLUTION *HLA-A* MISMATCHES ARE ASSOCIATED WITH SEVERE ACUTE GRAFT-VERSUS-HOST DISEASE AND INCREASED MORTALITY FOLLOWING UNRELATED DONOR TRANSPLANTATION FOR NONMALIGNANT DISORDERS

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High-resolution *HLA* mismatches (MM) have been consistently associated with poor outcomes following unrelated donor hematopoietic cell transplantation (URD-HCT) for malignancies. Nevertheless, the role of *HLA* matching in URD-HCT for nonmalignant disorders (NMD) has been poorly reported, and data on the impact of specific HLA-mismatches in the NMD setting is currently unknown. To address this gap, we evaluated 224 patients with NMD who underwent 10/10 or 9/10 URD-HCT from 2007 to 2021 at our center. The primary endpoint was overall survival (OS), whereas secondary endpoints included grade II-IV and grade III-IV (severe) acute graft-versus-host disease (aGVHD). High-resolution *HLA* typing was performed with SBT or NGS. Multivariable analyses were performed using Cox proportional hazards regression for OS and Fine-Gray competing risk regression for aGVHD. The median age was 10 years (range, 0-52), and the main indications for URD-HCT were Fanconi anemia (n=79; 35.3%), severe aplastic anemia (n=77; 34.4%), and Wiskott-Aldrich syndrome (n=15; 6.7%). All patients received bone marrow as the graft source, 95.1% had *in vivo* T-cell depletion with ATG, and 80.8% received cyclosporine + methotrexate as GVHD prophylaxis. Patient-URD pairs were divided into three groups: 10/10 (n=172), high-expression loci (HEL) 9/10 (*HLA-A, -B, -C*, or *-DRB1* MM; n=43), and low-expression loci (LEL) 9/10 (*HLA-DQB1* MM, n=9). In the multivariable regression, adjusted for confounders, mismatching at a single HEL-MM was associated with poor OS (HR=2.20; 95%CI=1.25-3.86; *P*=0.006), higher incidence of grade II-IV aGVHD (SHR=2.16; 95%CI=1.06-4.41; *P*=0.035), and a trend towards more severe aGVHD (SHR=2.41; 95%CI=0.9-6.48; *P*=0.08) compared to 10/10 matched pairs. In contrast, LEL-MM was not predictive of worse OS (HR=1.78; 95%CI=0.55-5.79; *P*=0.34), grade II-IV aGVHD (SHR=1.79; 95%CI=0.51-6.34; *P*=0.37), and severe aGVHD (SHR=1.85; 95%CI=0.3-11.35; *P*=0.51). Stratifying by the distinct HEL, only *HLA-A* MM (n=23) was significantly associated with inferior OS (HR=3.39; 95%CI=1.81-6.33; *P*=0.0001), higher incidence of grade II-IV aGVHD (SHR=3.81; 95%CI=1.74-8.34; *P*=0.0008), and increased severe aGVHD (SHR=4.73; 95%CI=1.7-13.22; *P*=0.003) in the

adjusted multivariable models. We performed a sensitivity analysis considering only the pediatric cohort (n=181), and HLA-A MM retained the association with increased mortality (HR=3.57; 95%CI=1.76-7.27; *P*=0.0004), higher occurrence of grade II-IV aGVHD (SHR=4.22; 95%CI=1.92-9.27; *P*=0.0003) and severe aGVHD (SHR=4.30; 95%CI=1.55-11.95; P=0.005), thus strengthening our results. This single-center study showed for the first time that *HLA-A* MM is highly detrimental in the URD-HCT for NMDs and should be avoided whenever possible. In addition, other HEL and LEL mismatches appear to be better tolerated and should be prioritized when a 10/10 *HLA*-matched URD is unavailable. Further studies with independent cohorts are warranted to validate our novel findings.