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ORAL ABSTRACTS

201.GRANULOCYTES, MONOCYTES, AND MACROPHAGES

Clinical Characteristics, Management, and Allogeneic Hematopoietic Cell Transplantation of Patients with Toll-like Receptor 8 Gain-of-Function Mutations

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Toll-like receptor 8 gain-of-function (TLR8 GOF) is a recently described inborn error of immunity due to germline or somatic mutations in the *TLR8* gene and characterized by severe neutropenia, infections, lymphoproliferation, humoral immune defects, and in some cases, bone marrow failure. Treatment of TLR8 GOF has been challenging to date, and guidance for optimal therapy is lacking. We describe the clinical characteristics and management of 10 patients with TLR8 GOF variants, including the first female patient and further clinical outcome on the 6 patients initially reported with this disease with a focus on the role of allogeneic hematopoietic cell transplantation (HCT).

All but one patient were male ranging from 0.5 months to 28 years at age of symptom onset. Eight patients had somatic mutations with variant allele frequencies of 7-26%; two patients had germline mutations. The 9 male patients all had severe neutropenia and varying degrees of anemia and/or thrombocytopenia. Oral ulcers, recurrent infections, hepatosplenomegaly, and hypogammaglobulinemia were common. Immune phenotype was variable, ranging from severe lymphopenia to marked T cell lymphoproliferation. Several patients had an inverted CD4:CD8 T cell ratio and skewing of T cell subsets to the terminal effector memory phenotype. Increased double-negative T cells were also observed. All patients had low class switched memory B cells. Bone marrows were hypo- to hypercellular with marked myeloid hypoplasia, and in most cases, with increased T cells, large granular lymphocytes, and/or lymphoid aggregates. Neutropenia was initially responsive to granulocyte colony stimulating factor (GCSF) +/- steroids in several patients but ultimately become refractory to therapy. Immunomodulatory agents and chemotherapy were unsuccessful. Six patients underwent allogeneic HCT; two patients died at 8 and 18 years without definitive therapy; and one patient was lost to follow-up. The female patient had germline disease and presented with pure red blood cell aplasia at 2 weeks of life and is scheduled to undergo HCT.

Transplant data were available for 5 of 6 patients who underwent HCT. Age at transplant was 3 to 21 years. One patient who received a graft from a 7/8 HLA-matched unrelated donor developed severe veno-occlusive disease and secondary graft failure. The patient underwent a second transplant and ultimately died. Another patient received a matched sibling donor HCT while critically ill from *Candida lusitaniae* and mucormycosis infection with associated multisystem organ failure. The patient engrafted with 100% donor chimerism but died on day +15 post-HCT. The remaining 3 patients are alive and well 8 months to 2 years post-HCT. Two patients received grafts from HLA-matched donors (1 sibling and 1 unrelated) with reduced intensity conditioning and cyclophosphamide, mycophenolate mofetil and vorinostat for graft-versus-host disease

(GVHD) prophylaxis. The third patient underwent a haploidentical HCT with myeloablative conditioning and post-transplant cyclophosphamide. Post-HCT complications included acute skin and/or gastrointestinal GVHD that was responsive to therapy in all patients, and severe lung GVHD in one patient. There were no major infectious complications. All three patients had full donor chimerism in myeloid and T cells with complete resolution of disease phenotype at last follow-up. The patient for whom detailed transplant data is not available received a haploidentical HCT. He developed mixed myeloid chimerism for which he received multiple donor lymphocyte infusions and was alive at last contact >3 years post-HCT.
TLR8 GOF should be considered in male and female patients with severe, unexplained neutropenia refractory to GCSF, and particular care should be taken when investigating for mutations given the disease-causing variant allele frequencies as low as 7%. Neutropenia and immune dysregulation were refractory to all therapies in our cohort, and TLR8 GOF was fatal in two patients who did not receive definitive therapy. Allogeneic HCT is curative and should be considered without delay for medically suitable patients.

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