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LETTER TO EDITOR

# Reduced Intensity Conditioning Allogeneic Transplant for SCID Associated with Cartilage Hair Hypoplasia

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To the Editor:

Cartilage-hair hypoplasia (CHH) is a rare inborn error of immunity which is inherited in an autosomal recessive pattern caused by pathogenic variants in the *RMRP* gene. CHH is associated with skeletal dysplasia, short stature, Hirschsprung disease, and varying degrees of immunodeficiency including combined immune deficiency (CID) and severe combined immunodeficiency (SCID) phenotypes (1, 2).

A recent prospective cohort study estimated that 24% of patients with CHH had humoral or combined immunodeficiency. Twenty-two percent of patients had progressive immunodeficiency over time. The primary cause of mortality in this cohort was immunodeficiency/dysregulation-related death including pneumonia, lung disease, and hematologic malignancies (1). Allogeneic hematopoietic stem cell transplantation (HSCT) is a curative therapeutic option for CHH. There have been few case series, but patients predominantly received a myeloablative conditioning regimen for treatment of a combined immunodeficiency (CID) phenotype (1). Data on outcomes following allogeneic HSCT for SCID phenotypes associated with CHH using a reduced intensity conditioning (RIC) regimen are limited. We herein report our experience with allogeneic RIC HSCT for SCID associated with CHH. We retrospectively reviewed records of all patients who underwent allogeneic HSCT for SCID associated with CHH at our institution with a RIC regimen containing alemtuzumab, fludarabine, and melphalan.

Six patients (4 male, 2 female) underwent allogeneic RIC HSCT for CHH at median age of 10 months (range, 5 months–4 years 11 months). Patients' demographic, HSCT course, and long-term immune reconstitution are shown in Table 1. Three patients were diagnosed through newborn screening for SCID and the other three were diagnosed for frequent infections and/or autoimmunity. All patients met primary immune deficiency treatment consortium (PIDTC) criteria for SCID prior to HSCT and all had biallelic mutations in the RMRP gene (3). Three of 6 patients were homozygous for mutation, n.71A > G. Patients received standard institutional antimicrobial prophylaxis and supportive care.

Patients received alemtuzumab 1 mg/kg over 5 days ($n = 4$) or 3 mg/kg over 4 days ($n = 1$) and fludarabine 5 mg/kg (weight < 10 kg, $n = 4$) or 150 mg/m$^2$ over 5 days ($n = 1$), and single dose of melphalan 4.7 mg/kg (weight < 10 kg, $n = 4$) or 70 mg/2 ($n = 1$, dose reduced by 50% for pre-existing sclerosing cholangitis with grade 3 liver fibrosis). All patients except one received RIC for the first HSCT. One patient received serotherapy only conditioning for initial HSCT but developed graft failure and subsequently received a RIC regimen for second HSCT. Patients received 8/8 human leukocyte antigen (HLA) matched ($n = 4$), or 1–2 allele mismatched ($n = 2$) bone marrow grafts based on high-resolution DNA typing of HLA-A, -B, -C, and -DRB1 alleles. Mismatched alleles were at HLA-B/-C and HLA-C for those two patients. Two patients received grafts from related donors. Graft versus host disease (GVHD) prophylaxis included cyclosporine and steroids.

Neutrophil recovery occurred a median of 12 days (range of 11–15 days) post-HSCT, and all but one patient initially engrafted with donor chimerism 95–100%. One patient engrafted with 92% initial donor chimerism. All but one patient subsequently developed mixed donor and recipient chimerism (Table 1). Lineage specific chimerism in these five patients demonstrated a median donor T-cell chimerism of 95% (range 82–99%) but lower median levels of donor chimerism in the myeloid and B-cell lineages of 45% (11–80.8%) and 4% (1.3–25%), respectively. Donor T-cell chimerism was stable in surviving patients, all with > 93% donor T-cell chimerism at last follow-up. Lineage-specific

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**Table 1** Description of 6 patients, with pre- and post-hematopoietic transplant (HSCT) characteristics. *RLD* restrictive lung disease, *RD* related donor, *URD* unrelated donor, *MUD* matched unrelated donor, *CMV* cytomegalovirus, *EBV* Epstein-Barr virus, *TRALI* transfusion-related acute lung injury, *SOS* sinusoidal obstruction syndrome, *ABS* absolute, *ARDS* acute respiratory distress syndrome, *TMA* thrombotic microangiopathy

| Characteristics | Patient 1 | Patient 2 | Patient 3 | Patient 4 | Patient 5 | Patient 6 |
|---|---|---|---|---|---|---|
| Sex | Male | Female | Male | Male | Female | Male |
| Age at HSCT | 8 mo | 4 yrs. 11 mo | 8 mo | 4 mo | 2 yrs. 11 mo | 11 mo |
| Age at last follow-up | 6 yrs | 7 yrs | 5 yrs | 5 yrs | 6 yrs. 11 mo | N/A |
| Weight, length/ height | 6.5 kg, 70.5 cm | 13.7 kg, 54.5 cm | 4.4 kg, 54.5 cm | 5.7 kg, 54.3 cm | 6.2 kg, 56 cm | 4.5 kg, 47.4 cm |
| RMRP mutation | Homozygous r.-5delins8 | Homozygous n.71A > G | Allele 1: n.-24_-10dup<br>Allele 2: n.147G > A | Homozygous n.71A > G | Homozygous n.71A > G | Allele 1: n.-425 > A<br>Allele 2: n.-432 T > C |
| Pre-transplant complications | MSSA bacteremia<br>CMV pneumonitis | Recurrent PNA<br>Chronic hepatitis<br>Sclerosing Cholangitis | Pre-mature 32 weeks | None | None | Hirschsprung's disease s/p ileostomy<br>Thoracic dystrophy w/ RLD |
| Donor HLA match | RD, 8/10 | MSD, 10/10 | URD, 10/10 | URD, 10/10 | URD, 7/8 | MUD, 10/10 |
| Stem cell source | Bone marrow | Bone marrow | Bone marrow | Bone marrow | Bone marrow | Bone marrow |
| TNC/kg (10^8) | 10 | 10 | 10 | 10 | 10 | 14.8 |
| Post-transplant | | | | | | |
| Neutrophil recovery (ANC > 500) (days) | 12 | 13 | 15 | 12 | 11 | 12 |
| Acute GVHD | None | None | None | None | Gr 2 skin | Gr 2 skin, gut |
| Viremia | CMV | Adenovirus<br>EBV | None | CMV<br>EBV | CMV<br>EBV | Adenovirus |
| Other complications | TRALI reaction with stem cell infusion | SOS, Norovirus enteritis | None | AIHA | None | Candidemia<br>Ileostomy prolapse |
| Last follow-up post-HSCT | 5 yrs | 2 yrs | 4 yrs. 11 mo | 4 yrs. 5 mo | 4 yrs | N/A |
| Donor chimerism | T-cells: 93.7%<br>B-cells: 32%<br>Myeloid: 1.3% | T-cells: 99%<br>B-cells: 80.8%<br>Myeloid: 18.6% | T-cells: 96%<br>B-cells: 70%<br>Myeloid: 4% | T-cells: 95%<br>B-cells: 45%<br>Myeloid: 25% | Whole blood: 100% | T-cells: 82%<br>B-cells: 11%<br>Myeloid: 5% |
| ABS CD3 | 1,588 | 813 | 1,887 | 3,521 | 4,441 | N/A |
| ABS CD4 | 825 | 549 | 824 | 2,092 | 2,034 | N/A |
| CD4 naïve % | 49.1% | 56.6% | 43.7% | 74.8% | 62% | N/A |
| ABS CD8 | 624 | 244 | 821 | 1,343 | 2,203 | N/A |
| ABS CD19 | 509 | 189 | 256 | 85 | 616 | N/A |
| PHA (cpm) | 264,587 | 302,216 | 365,451 | 333,907 | 240,597 | N/A |
| IgG/IgA/IgM(mg/dl) | 1,070/168/112 | 548/126/326 | 820/80.4/43.7 | 475, < 6.6/ < 5 | 1020/122/124 | N/A |
| Off IgG replacement | Yes | Yes | Yes | No | Yes | N/A |
| Current status | A & W | A & W | A & W | A & W | A & W | Died D + 85 multisystem organ failure secondary to sepsis, ARDS, ileus, abdominal compartment syndrome, TMA |

donor chimerism details at last follow are shown in Table 1. One patient with pre-existing sclerosing cholangitis and liver fibrosis developed sinusoidal obstruction syndrome (SOS) documented by ultrasound and Doppler examination of the liver on day + 78 that resolved with steroid and defibrotide therapy. One additional patient received steroid due to clinical concern for SOS, which is the practice at our institution based on weight gain, abdominal pain, and rising bilirubin despite normal ultrasound findings. Two patients (33%) developed acute skin GVHD one with concurrent gut GVHD but no patient developed grade 3–4 GVHD. Additionally, one patient developed limited chronic skin GVHD. CMV viremia occurred in three patients (50%), EBV viremia in three patients (50%), adenoviremia in one patient (17%), and norovirus enteritis in one patient (17%). All but one patient has isolated viremia after transplant; one patient with adenoviremia had adenovirus identified in the stool. One patient (17%) developed autoimmune hemolytic anemia that resolved with steroids and rituximab therapy. Survival in our cohort was 83% (5 of 6 patients) with a median follow-up of 4.5 years post-transplant (range, 2–5 years). One patient died on day + 85 from multi-system organ failure secondary to sepsis, acute respiratory distress syndrome, ileus, abdominal compartment syndrome, pneumoperitoneum, and thrombotic microangiopathy. Contributing factors included Hirschsprung's disease with post-surgical complications following ileostomy and restrictive lung disease from severe thoracic dystrophy. All five surviving patients achieved excellent T-cell reconstitution, as demonstrated by normal absolute CD4 counts, normal CD4 naïve cell counts, and normal responses to PHA. Four of the five surviving patients (80%) achieved adequate B-cell immune reconstitution and no longer require IgG replacement.

This study evaluates the outcomes of a uniform RIC regimen containing alemtuzumab, fludarabine, and melphalan in children undergoing allogeneic HSCT for SCID associated with CHH. Our experience suggests that RIC HSCT with a bone marrow graft can be curative, and offers durable T-cell engraftment, low rates of GVHD, and survival greater than 80%. Earlier study performed reported an overall survival of 62.5% in 16 patients who underwent HSCT for CHH with mostly a CID phenotype and received primarily a myeloablative regimen containing busulfan and cyclophosphamide; however, supportive measures have improved since this time and thus may have affected outcomes (2). Ip et al. reported an overall survival of 83% in 13 patients who underwent HSCT for CHH with variable clinical phenotype including 3 patients with SCID (4). Most patients (10/13) received RIC with treosulfan/fludarabine or fludarabine/melphalan, which supports better outcomes with a RIC regimen. We observed a high incidence of mixed chimerism, which has been reported before by our group with this regimen in patients undergoing HSCT with SCID (5). Notably, all surviving patients experienced T-cell reconstitution and maintained donor T-cell chimerism greater than 90%, which is the critical lineage in SCID. This is not surprising given the survival advantage of donor-derived T-cells in the setting of SCID. Despite variable donor B-cell chimerism, patients achieved B-cell reconstitution and independence from IgG replacement; the one patient who continues IgG replacement received rituximab for AIHA, which may be a major contributory factor for lack of B-cell reconstitution. No patient developed grade 3–4 GVHD likely due to effective in vivo T-cell depletion of the graft with alemtuzumab (5). Furthermore, RIC-HSCT was well tolerated with low incidence of toxicity. Risk of toxicity is especially important when evaluating which conditioning regimen to use as CHH with SCID is discovered on newborn screens more frequently. A RIC regimen allows us to limit toxicity in comparison to a myeloablative regimen. Unlike with a CID phenotype, the risk of graft rejection is lower in SCID, which further supports using a RIC regimen. Surviving patients remain clinically well without significant infections or autoimmunity. Despite the high incidence of mixed chimerism with this regimen, our experience suggests that RIC HSCT appears to be curative for SCID in CHH. Longitudinal follow-up is needed to determine if this T-cell reconstitution and function will be maintained, and if the mixed myeloid and B-cell chimerism influences the risk of malignancy or other disease comorbidities.

**Author Contribution** All authors have contributed to the manuscripts in significant ways and have reviewed and agreed upon the manuscript contents.

**Data Availability** My manuscript has no associated data.

## Declarations

**Ethics Approval** Obtained.

**Consent to Participate** Obtained.

**Consent for Publication** Obtained.

**Conflict of Interest** The authors declare no competing interests.

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