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721.ALLOGENEIC TRANSPLANTATION: CONDITIONING REGIMENS, ENGRAFTMENT AND ACUTE TOXICITIES

Allogeneic Bone Marrow Transplantation from HLA-Identical or Haploidentical Donors for Children and Adolescents with Sickle Cell Disease: A Feasible Curative Option

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The only curative option widely available for sickle cell disease (SCD) is bone marrow transplantation (BMT). Since few patients have a healthy matched sibling donor (MSD), haploidentical (haplo) donors have expanded the donor pool to approximately 90% of the patients. The addition of thiotepa to the Johns Hopkins conditioning therapy backbone dor haplo BMT showed durable engraftment and excellent overall survival. However, graft rejection has remained an important obstacle. Our challenge in these patients has been to augment the conditioning therapy to provide adequate engraftment, while maintaining a low transplant-related mortality. **Methods**: Retrospective data of all 26 patients with SCD followed by our group after MSD (n=7) and haplo (n=19) BMT performed in four different institutions. With a MSD, conditioning was rATG 4.5mg/kg, Busulfan (Bu, AUC 4,500), Fludarabine (Flu, 120mg/m²) or rATG, Bu, Cyclophosphamide (Cy, 200mg/kg) and with haplo donors, rATG 4.5mg/kg, Thiotepa 10mg/kg, Flu 150mg/m², Cy 29 mg/kg and TBI 2Gy. Patients were prepared to BMT with intense hypertransfusion/bleeding or erythrocytapheresis to keep HbS<30 and Hb˜10g/dL, reticulocytes <10% for 2-3 months prior to BMT, with intensive chelation to keep ferritin <1,000ng/mL. The presence of donor specific antibodies would exclude the patient from undergoing BMT. Due to two consecutive secondary graft failures (no detectable donor cells despite initial engraftment) and two falling mixed chimerism among the first 13 patients undergoing haplo, the doses of the conditioning therapy were increased to Cy 50 mg/kg and TBI 4Gy in a single fraction, as previously used in our patients with aplastic anemia undergoing BMT. Six consecutive patients received this augmented conditioning therapy. All patients had serial chimerism measured by STR. The graft-versus-host disease (GVHD) prophylaxis included Cyclosporine - Methotrexate in MSD and post-transplant Cy/mesna, mycophenolate mofetil and sirolimus in haplo. **Results**: Between September 2016 and April 2023, 26 patients underwent BMT, with a median age of 11 years (4-20), half of them females, 7 with a MSD and 19 an haplo (4 siblings, 6 fathers, and 9 mothers); 77% of the donors had sickle cell trait. The graft was bone marrow in all but one patient with Sb thal and Hodgkin's lymphoma. The median follow-up was 15.5 months. All patients engrafted. BMT with MSD had excellent outcomes and stable chimerism. Among the first 13 patients undergoing haplo, secondary graft failure occurred very suddenly in two patients (CD34 cell doses of 2 and 8x10 ^{6} CD34/kg), both male teenagers; two additional patients had a significant drop in chimerism up to 30% donor cells but responded to serial donor leukocyte infusions 1-5 x10 ^{6} CD3/kg (2 and 6) and developed very mild skin GVHD. The other patients maintained > 89-100% donor cells. Thereafter, with the augmented conditioning regimen, all six consecutive patients have stable 100% donor chimerism. Acute II-III GVHD was observed in 34% and chronic GVHD in 15% of the patients. Viral reactivations (CMV, HHV6, BKV, HHV7 and EBV) were observed in all patients. Overall survival is 100% and rejection-free survival is 83% at 1 year (Figures 1, 2). **Conclusions**: Allogeneic BMT with an HLA-identical

or haploidentical family donor was feasible to treat SCD with an excellent overall survival. With a larger cohort and longer follow-up, the long-term effects of this strategy will be thoroughly studied.

Disclosures No relevant conflicts of interest to declare.

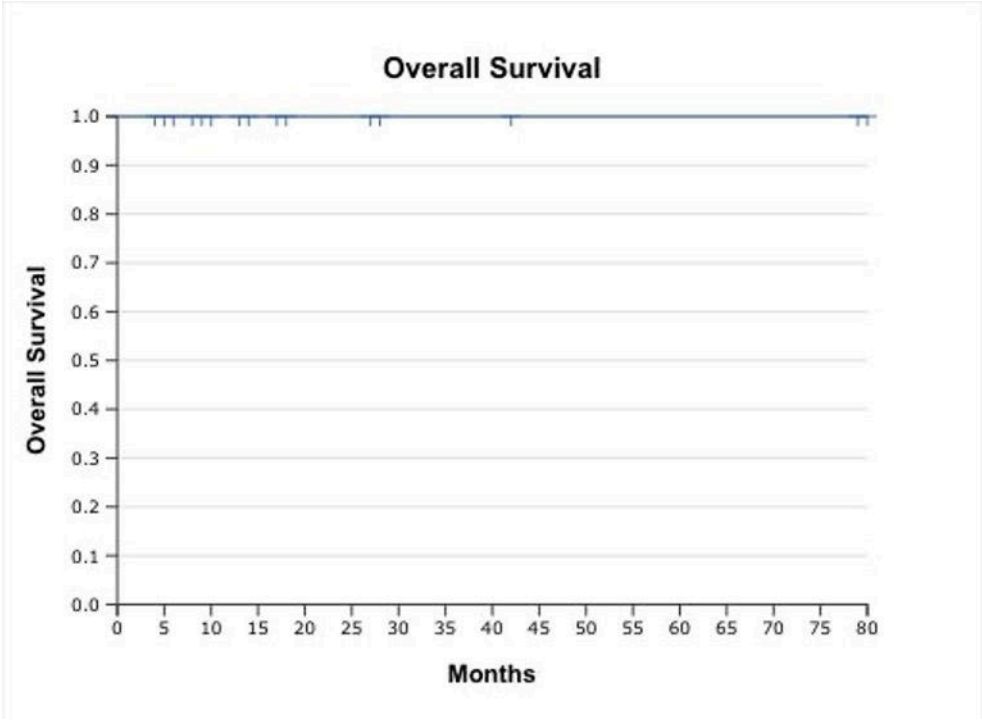

Figure 1

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