Abstract: S293

Title: HYDROXYCARBAMIDE & HYPERTRANSFUSION PRE-CONDITIONING LEADS TO HIGH RATES OF CURE & ABROGATES GRAFT FAILURE IN REDUCED INTENSITY PTCY HAPLOIDENTICAL TRANSPLANTATION IN CHILDREN WITH SICKLE CELL DISEASE

Abstract Type: Oral Presentation

Session Title: Sickle cell disease

Background:

Post-transplantation cyclophosphamide (PTCy) has enabled transplantation across the HLA barrier using reduced intensity conditioning. This constitutes a very important development for non-malignant conditions affecting populations poorly represented in the donor registries and with end-organ damage, like sickle cell disease. Whilst both the Vanderbilt Global Haploidentical Learning Collaborative for a Cure (VGC2) and BMT CTN 1507 trial have shown in adults' outcomes and toxicity equivalent to related transplantation, the benefit to the paediatric population has been limited due to high primary and secondary graft failure rates (Kassim, ASH 2022; Kassim, ASH 2023).

Aims:

We hypothesized that adding pre-conditioning with hydroxycarbamide 30 mg/kg (adjusted for cytopenias) and hypertransfusions (two-weekly transfusion to maintain Hb >100 g/L) for a minimum of eight weeks pre-transplantation would abrogate the risk of graft failure due to the expanded haemopoietic compartment in children without increasing toxicity.

Methods:

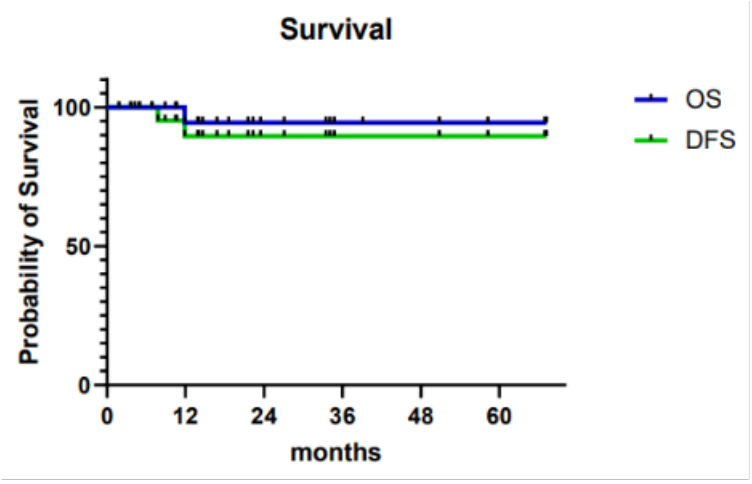
From August 2017 to October 2023, twenty-six consecutive patients received a RIC haploidentical HCT with PTCy. The conditioning included ATG (Genzyme) 0.5 mg/kg day -9 and 2 mg/kg days -8 and -7 (total dose 4.5 mg/kg), thiotepa 10 mg/kg day -7, fludarabine 30 mg/m2 days -6 to -2 (total dose 150 mg/m2), cyclophosphamide 14.5 mg/kg days -6 and -6 (total dose 29 mg/kg) and TBI 2 Gy on day -1. GVHD prophylaxis consisted of two doses of cyclophosphamide 50 mg/kg on days +3 and +4, MMF from day +5 until day +35 and sirolimus targeting 10 - 15 ng/mL from day +5 until cessation of immunosuppression (de la Fuente, BBMT 2019). The median age was 12.4 years (2-16). The median cell dose was 4.04 x 108 TNC/kg 4.04 (range: 1.62-23.56) and 4.7 x 106 CD34+/kg (range: 1.79-17.94). Patients were transplanted for stroke, severe cerebrovascular disease, or recurrent vaso-oclusive crises and/or acute chest syndrome not responding to hydroxycarbamide. The source of stem cells was bone marrow. Median survival was 17.7 months (1.8 – 67.2).

Results:

All patients engrafted and achieved evidence of donor haemopoiesis on day +28 and established normal haemopoiesis with resolution of the sickle related manifestations. Median neutrophil engraftment occurred on day +21 (15 – 29) and platelets reached >50 x 109/L on day +41 (26 – 69). There was one case of secondary graft failure at 6 months (3.8%). Whilst there was a degree of mixed chimerism on day +28 (>95% donor: 84% in whole blood & 63.6% in T cells; 90% to 94% donor: 16% in whole blood & 13.6% in T cells; 50% to 89% donor: 18.3% in T cells; <50% donor: 4.5% in T cells), all but one of the patients were >95% donor in both whole blood and T cells at a year post-transplantation and off immunosuppression. There was one death (3.8%), on day +361 due to pneumococcal sepsis in a patient not taking penicillin V prophylaxis in a patient otherwise off immunosuppression with donor haemopoiesis and no GVHD. There were no cases of VOD. The Kaplan-Meier 2-years OS was 94.4% and the disease-free survival was 89.6% (figure 1).

Acute GvHD ≥ grade 2 occurred in 8 patients (30.8%) whilst grade III-IV was 3 (11.5%). Chronic mild GvHD occurred in 3 patients (11.5%) and moderate/severe in 4 patients (15.4%). Chronic GVHD was resolved in all

patients by 18 months. aGVHD grade IV was only 1% (3.8%) and severe cGVHD 1% (3.8%). The median time to cessation of immunosuppression was 201.5 days (151-560).



Summary/Conclusion:

In conclusion, PTCy with a reduced intensity conditioning regimen in conjunction with hydroxycarbamide & hypertransfusions pre-conditioning leads to high rates of cure abrogating the risk of graft failure and has low toxicity in the paediatric population, akin to the outcomes seen in adults with sickle cell disease.

Keywords: Sickle cell disease, Haploidentical stem cell transplantation, Reduced intensity transplantation, Children