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Clinical Outcome after Adoptive Infusion of BPX-501 Cells (donor T cells transduced with iC9 suicide gene) in Children with Thalassemia Major (TM) Given Alfa/Beta T-Cell Depleted HLA-Haploidentical Stem Cell Transplantation (HSCT)

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Background: Allogeneic HSCT from either an HLA-identical sibling or an unrelated donor is largely used as potentially curative treatment in patients with TM. So far, the experience of HLA-haploidentical HSCT in TM is much more limited and the reported probability of thalassemia-free survival is lower than that of patients given conventional transplants. In the last 5 years, we developed a novel method of selective T-cell depletion of the graft based on removal of α/β T cells (ClinicalTrial.gov identifier: NCT01810120), which was shown to be safe and effective in children with non-malignant disorders. To further optimize the approach by accelerating the recovery of adaptive immunity, we designed an ongoing phase I/II trial aimed at testing the safety and efficacy of post-transplant infusion of BPX-501 cells in children with malignant or non-malignant disorders (ClinicalTrials.gov identifier: NCT02065869). BPX-501 cells can be tracked easily in patient peripheral blood since they are CD3/CD19 positive. We report on 5 children with TM who were enrolled in the phase II of the study.

Patients and Methods: All these 5 children (median age 10 years, range 3-12) were transfusion-dependent and were given iron-chelation therapy before haplo-HSCT. One patient belonged to class I and 4 to class II of the Pesaro classification. In all patients, the conditioning regimen consisted of a combination of busulfan (16 mg/Kg), thiotepa (10 mg/Kg) and fludarabine (160 mg/sqm). Rabbit ATG (12 mg/Kg over 3 days, from day -4 to day -2) and Rituximab(200 mg/sqm on day -1) were administered to prevent GvHD/graft failure and EBV-related lymphoproliferative disorders, respectively. No post-transplantation graft-versus-host disease (GvHD) prophylaxis was administered. Three of the 5 patients have a follow-up longer than 60 days and are reported in detail.

Results: All 3 evaluable patients engrafted, reaching full donor chimerism; none experienced either acute or chronic GVHD, or organ inflammatory-related toxicity. BPX-501 cells were infused on day +12, +17 and +13 after transplantation, respectively. None of the children were re-hospitalized after initial discharge. The last erythrocyte transfusion in the 3 evaluable patients was administered on day + 24, 18 and 17, respectively. BPX-501 cells expanded after infusion and are still persisting at last follow-up. All children are alive and transfusion-independent at day +90, +62 and +61, respectively. The blood cell counts at last follow-up are shown in Figure 1.

Figure 1

	Day post HSCT	Hb gr/dL	CD3+/μL	CD4+/μL	CD8+/μL	CD3 + CD19+/μL
Patient #1	90	11.9	350	116	103	35
Patient #2	62	10.9	246	89	120	3
Patient #3	61	10.7	200	64	115	29

Conclusions: Children with TM can benefit from curative haplo-HSCT after depletion of α/β T cells followed by infusion of BPX-501 cells, which contribute to speed immune recovery of adaptive T-cell immunity, thus rendering the procedure safer. Further follow up will be presented at the meeting.

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Analytical Validation of a Relative Average Telomere Length Assay in a Donor Population for Hematopoietic Stem Cell Transplant (HCT)

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Donor average telomere length was recently found to be associated with survival in severe aplastic anemia patients who undergo unrelated donor HCT. Telomere length may also be clinically useful in selecting donors for other cancer patients who undergo HCT. To that end, we have validated an advanced multichrome quantitative-PCR assay that can precisely and reproducibly measure the relative average leukocyte telomere length (rATL) using two single copy genes as the reference. Whole blood samples from 319 healthy donors were obtained from the Center for International Blood and Marrow Transplant Research (CIBMTR). This multichrome multiplex relative average telomere length assay showed inter-assay coefficients of variance (2.6%). The precision of measuring telomere length for 319 donor samples, over 5 days, between 6 different assays, show an overall coefficient of variance of less than 3%.

The mean rATL (T/S ratio) for the donor population tested was 1.06, with a range of observed 0.67 to 3.46 (T/S ratio). In comparison, rATL T/S ratio reference range obtained from a normal healthy population of 504 subjects had a range of 0. 58 to 1.55. The differences are not statistically significant. The availability of a precise and reproducible rATL assay will enable further research and clinical investigations relating to donor selection for cancer patients requiring HCT.

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Predictive Value of Absolute Lymphocyte Count at Day 30 Post-Allogeneic Transplantation for Early Mortality Irrespective of GVHD Prophylaxis

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