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Outcomes of Unrelated Donor Hematopoietic Stem Cell Transplantation for Pediatric Patients: The First Report From Iran

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Introduction: The availability of HLA registries and also Cord Blood banks has expanded the application of HSCT. Although HSCT has 25 years of history in Iran, a majority of transplants performed until 10 years ago has been either autologous or from related donors. The reason has been the unavailability of HLA registry and rich cord blood banking in the country. This trend has changed over the last 10 years after an independent pediatric HSCT unit was created, which considerably boosted the number of transplants from unrelated donors (URD) and also umbilical cord blood (CB). In this study we report the transplant outcomes for pediatric patients with malignant and non-malignant disorders undergoing matched or mismatched URD transplantation.
Material and Methods: Eighty six patients (53 male, 33 female) aged <15 years old (Mean: 6.30 years) who had received 89 HSCT from unrelated donors at pediatric wing of Hematology-Oncology and Stem Cell Transplantation Research Center (HORCSCT) were enrolled (45 full HLA-matched donor HSCTs, 50.6%). Stem cell sources were bone marrow (BM) in 24, peripheral blood (PB) in 24 and CB in 41 transplants. Underlying disorders for HSCT were mostly Primary Immunodeficiency Disorders, Acute Leukemia, Fanconi Anemia and Major Thalassemia. We evaluated graft-versus-host-disease (GvHD), overall survival (OS) and disease free survival (DFS).
Results: Primary graft failure reported in 13/89 that occurred only in patients transplanted from CB stem cell ($P < .001$) and 8/89 experienced graft rejection. Acute GvHD grade I-II occurred in 33.3%, 41.7% and 22% and grade III-IV in 54.2%,25% and 29.3% of patients who received PB, BM and CB transplantation respectively (*P*-value: .002). With a median follow up of 25 months, OS was 75%, 70.8% and 41.5% in PB, BM and CB stem cell transplantation respectively.
Conclusion: Although survival with unrelated umbilical CB stem cell transplant is suboptimal, the outcomes of transplants from PB and BM stem cell is acceptable and is comparable to those from related donors. Our results confirm the potential benefit of using URD hematopoietic stem cells for allogeneic transplants and highlight the importance of HLA registry expansion and also development of international relations. Of note according to our umbilical CB stem cell transplant result, and as haploidentical stem cell transplant is increasing around the world, in our opinion it may be better to lessen umbilical CB stem cell transplant.

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LONG TERM Outcomes of Pediatric Patients with Malignant and NON-Malignant Disorders Receiving A/B T-CELL Depleted HLA-Haploidentical Hematopoietic STEM CELL Transplantation (HSCT) Followed by Infusion of BPX-501 T CELLS (DONOR T CELLS Transduced with IC9

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Allogeneic HSCT is curative for pediatric hematopoietic disorders such as malignancies, immune disorders, hemoglobinopathies and bone marrow failures. For patients lacking an HLA-matched donor, haploidentical family members represent a potential alternative. Ex vivo T-cell depletion of haploallografts reduces risk of GvHD, but increases risk of lethal infections. BPX-501 is a donor T cell product, infused after transplant to improve immune reconstitution. To avoid GVHD, BPX-501 T cells are transduced with a safety switch activated by the drug rimiducid (AP1903), with truncated CD19 so $CD3^+/CD19^+$ T cells can be tracked.
The ongoing BP-004 phase I/II trial (Bellicum Pharmaceuticals; NCT02065869) is an international trial in patients receiving _/_ T-cell depleted (CliniMacs) HLA-haploidenticalHSCT infusion of BPX-501 at 2 weeks. All patients received myeloablative therapy, and low dose ATG prior to transplant. No GVHD prophylaxis was given. In Phase 1, cohorts of 3 each received 2×10^5, 5×10^5 and 1×10^6 cells/kg BPX-501, respectively. The Phase 2 maintains the 1M cell dose/kg for all patients in the US, and for non-malignant patients in the EU, while malignant patients in the EU have escalated to 2×10^6/kg and 4×10^6 cells/kg.
90 evaluable patients have undergone _/_ T-cell depleted HSCT with infusion of BPX-501. We report 69 evaluable patients with follow-up ≥100 days and 33 evaluable patients with ≥1 year followup. 40 non-malignant patients (e.g. 9 SCID, 2 HLH, 7 Fanconi anemia, 5 WAS, 7 Thalassemia major B^0B^0) and 29 malignant patients are reported. Median age for malignant patients was 6.6 (.8-18.2) years, and for non-malignant patients 3.9 (.1-21.9) years. Median time to engraftment was 16 (9-35) days with median discharge of 26 (14-180) days. There was low TRM (2.8%).
21 patients had acute GVHD 1-3 (overall 30%): 17 with Grade 1; 3 with Grade 2, 1 with Grade 3 and no Grade 4. Mild cGVHD was seen in 2 patients, and one case of severe cGVHD in a malignant patient, attributed to the allograft, rather than BPX-501 T cells. Rimiducid was used in 4 of these patients with Grade 2 or 3 aGVHD and resulted in rapid resolution of symptoms. Rimiducid was also used in the severe cGVHD case with partial response.
Immune reconstitution was brisk in malignant and non-malignant patients. CD3, CD4, CD8 and B cells noted in Figure 1. CD3+CD19+ cells were detectable at 1 year via flow cytometry from peripheral blood (range .33-1339 cells/ul). Outcomes from selected patient populations: a.) in primary immune deficiency patients, cellular and immunoglobulin levels were normalized b.) in WAS patients, 100 day platelet counts were in normal range (Figure 2) and c.) in

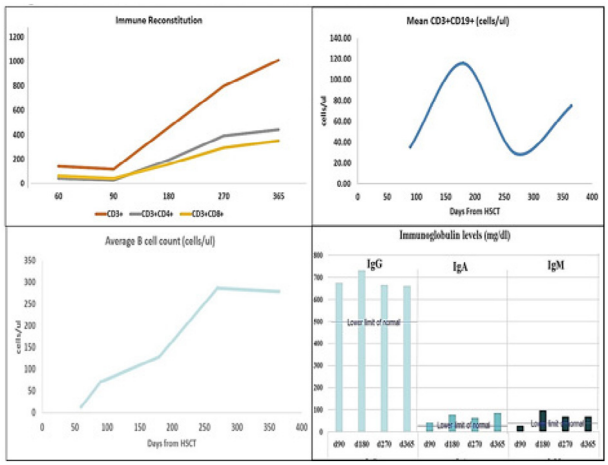

Figure 1. Immune Reconstitution in BP-004 Patients.

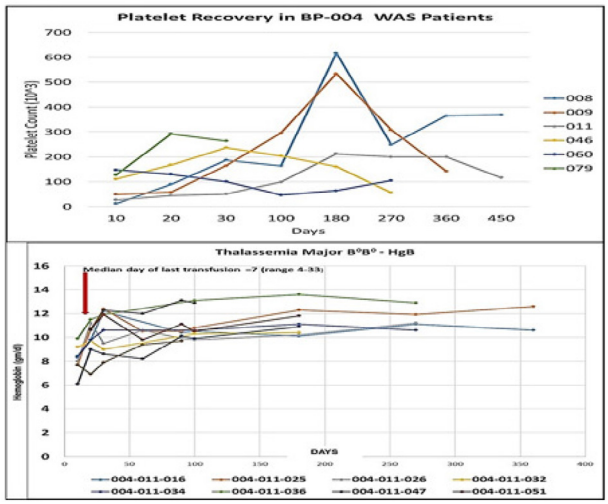

Figure 2. Selected Outcomes in BP-004 Patients.

hemoglobinopathy patients, day 100 hemoglobin values were in normal range (Figure 2). The low TRM and GVHD outcomes in BP-004 support _/_ depleted haplo-transplant with BPX-501 T cell infusion as a therapeutic approach for patients lacking a matched donor.

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Unmanipulated Haploidentical Transplants Using Post-Transplant Cyclophosphamide CAN Safely Extend Hematopoietic STEM CELL Transplantation for Patients Without an HLA Matched DONOR: Preliminary Results in Brazil

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Finding a compatible HLA donor is still a limitation for certain patients, especially ethnic minorities or racially mixed populations commonly found in Latin America countries. The use of cyclophosphamide post-transplant for HLA-haploidentical donor transplantation eliminate alloreactive cells without T cell depletion. This strategy has been expanding due to the low cost and for sparing regulatory T cells and non-dividing hematopoietic stem. Some recent data suggesting that survival of patients after BMT haploidentical with cyclophosphamide post-transplant is comparable with MUD transplantation for some malignancies.

Objective: To compare the results of haploidentical bone marrow transplantation (BMT Haplo) with HLA compatible 10×10 related donor transplantation (BMT MRD) and HLA compatible 10×10 unrelated (BMT MUD) with respect to overall survival, relapse rate, mortality, engraftment rate and incidence of acute graft-versus-host disease (GVHD).

Methods: Retrospective analysis of adult and pediatric patients undergoing first transplant of hematopoietic stem cells with a diagnosis of acute leukemia, myelodysplastic syndrome and myeloproliferative neoplasms in the period of 2010-2015 at a private Hospital in Brazil.

Results: We analyzed 18 patients undergoing BMT Haplo, 26 patients with BMT MRD and 38 patients undergoing BMT MUD. The 3 groups were comparable in age and underlying pathology. The median follow-up was 35 months. Overall survival at 3 years was 45.2% for BMT Haplo, 52.8% for BMT MRD and 43.3% for BMT MUD ($P = .37$). There was no graft failure in the 3 groups. The cumulative incidence of relapse at one year was 33.2% for BMT Haplo, 23.9% for BMT MRD and 27.8% for BMT MUD, with $P = .65$. Recurrence-free survival at 3 years was 40.4% for BMT Haplo, 41.4% for BMT MRD and 34.8% for BMT MUD ($P = .77$). The non-related mortality relapse within 1 year was comparable in the 3 groups: 26.4% for Haplo, 16.2% for MRD and 27.5% in BMT MUD, $P = .40$. There was a trend toward less incidence of acute GVHD grade III-IV until D+180 in BMT Haplo (5.6%) compared to BMTMRD (21%) and BMT MUD (33%), $P = .06$.

Conclusions: No significant differences were found between haploidentical and HLA-match transplant outcomes. Use of cyclophosphamide post-transplant resulted in a high rate of stable engraftment and a low risk of graft versus host disease (GVHD). In developing countries, technology of graft manipulation has been a limitation for haploidentical transplants. At this moment a prospective multicenter trial on unmanipulated haploidentical transplant is being formulated in Brazil. Our preliminary results suggest that unmanipulated haploidentical transplant has overcome the issues of technology and costs and can be an option for patients without an HLA matched donor.

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Comparison of Single Unmanipulated Umbilical Cord Blood or Co-Infusion of an Umbilical Cord Blood Graft with CD34+ Cells From a Third Party Donor in Adults with Acute Leukemia

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