Reduced-Intensity Stem Cell Allografting for PNH Patients in the Eculizumab Era: The Mexican Experience

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Background: Paroxysmal nocturnal haemoglobinuria (PNH) presents as two major entities: the classical form, predominantly hemolytic, and a secondary type with marrow failure and resultant aplastic anaemia (AA-PNH). Currently, the treatment of choice of the hemolytic variant is eculizumab; however, the most frequent form of PNH in México is AA-PNH.

Patients and Methods: Six consecutive AA-PNH patients with HLA-identical siblings were allografted in two institutions in México, employing a reduced-intensity conditioning regimen for stem cell transplantation (RIST) conducted on an outpatient basis.

Results: Median age of the patients was 37 years (range 25–48). The patients were given a median of $5.4 \times 10^6$/kg allogeneic CD34(+) cells, using 1–3 apheresis procedures. Median time to achieve above 0.5 $\times 10^9$/l granulocytes was 21 days, whereas median time to achieve above 20 $\times 10^9$/l platelets was 17 days. Five patients are alive for 330–3150 days (median 1437) after the allograft. The 3150-day overall survival is 83.3%, whereas median survival has not been reached, being above 3150 days.

Conclusion: We have shown that hypoplastic PNH patients can be allografted safely using RIST and that the long-term results are adequate, the cost–benefit ratio of this treatment being reasonable. Additional studies are needed to confirm the usefulness of RIST in the treatment of AA-PNH.

Ibrutinib Treatment of Relapsed CLL Following Allogeneic Transplantation: Sustained Disease Response and Promising Donor Immune Modulation

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**Background & Methods:** Treatment of relapsed chronic lymphocytic leukemia (CLL) with ibrutinib results in high rates of progression-free and overall survival. Ibrutinib, an irreversible Bruton’s tyrosine kinase inhibitor, may also modulate donor T cell alloimmunity via interleukin-2-inducible kinase inhibition. We report results of ibrutinib salvage therapy in 5 high risk CLL patients who relapsed following allogeneic hematopoietic cell transplantation (allo-HCT). Lymph node (LN) size was measured by CT scan, CLL minimal residual disease (MRD) levels by IgH high-throughput sequencing (HTS) (ClonoSIGHT™ test, Sequenta Inc.), donor CD3 chimerism by short tandem repeat analysis, and donor B cell immune reconstitution by IgH HTS quantification of total IgH molecules and unique IgH clonotypes.

**Results:** All 4 patients with pathologic lymphadenopathy prior to treatment experienced dramatic LN reduction on ibrutinib (Fig 1A; 68% average reduction after 3 mos). Patients SPN3975 (17p del) and SPN3431 (11q del) achieved undetectable CLL MRD (<10⁻⁶) after 39 mos and 8 mos, respectively (Fig 1B, 1C). SPN3975 had failed to maintain full donor CD3 chimerism after dose-escalated donor lymphocyte infusions but after 1 yr of ibrutinib achieved full donor chimerism. Oral and skin chronic graft-versus-host disease (cGVHD) additionally resolved after 6 mos. Two additional patients have increased donor chimerism since starting ibrutinib. Although SPN3975 has not taken ibrutinib for >10 mos, full donor chimerism persists and CLL MRD remains undetectable (Fig 1B). Prior to ibrutinib, donor B cells in this patient (excluding the CLL clone) accounted for ∼0.2% of total PBMC. Following discontinuation of ibrutinib, donor B cells increased within 6 mos and now comprise >1% of PBMC (Fig 1D). Furthermore, recovering B cells have diverse, low frequency IgH clonotypes (Fig 1E).

**Conclusions:** Ibrutinib provides effective salvage therapy for CLL relapse following allo-HCT and demonstrates promising donor immune modulation, promoting full donor chimerism and cGVHD resolution. Here we present 2 post allo-HCT CLL relapse patients who achieved MRD negativity on ibrutinib, one of whom maintains undetectable CLL 10 mos after stopping therapy. Our findings show rapid, sustained, and diverse immune reconstitution without CLL recurrence following discontinuation. Clinical trials are needed to determine the duration of therapy for post allo-HCT relapse, role of ibrutinib maintenance, and cGVHD treatment efficacy.

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**High Disease-Free Survival (DFS) Supports Continued Investigation of Double-Unit Cord Blood Transplantation (DCBT) in Children with High-Risk Acute Leukemia Especially in the Setting of Single Units with Low Dose and/or a High Degree of HLA-Mismatch**

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**Introduction:** DCBT in children with acute leukemia is controversial given the findings of the recent BMT CTN randomized study. However, many children will not have adequate single-units based on the recent CIBMTR analysis (cryopreserved TNC > 3.0 x 10⁷/kg and 6-8/allele donor-recipient HLA-match).

**Methods:** We analyzed 35 consecutive pediatric DCBT patients treated for acute leukemia (10/2005-2/2013). All CBT recipients in this period received 2 units.

**Results:** Median pt age was 7.5 yrs (range 0.8-18), median weight was 28 kg (range 8-75), and 69% had non-European ancestry. Seventeen pts had AML: 6 CR1 (one each with M7, secondary 5q- MDS, FLT-3 ITD, Ph+), Down syndrome MRD+, germline mutation CEBPa), 8 CR2, 1 CR3, and 2 in aplasia. Seventeen pts had ALL: 10 CR1 [3 Ph+ (one MRD+), 2 T-cell ALL, 1 MLL, 1 L3 disease, and 3 multiple inductions, 4 CR2, CR3. One pt had advanced CML Conditioning was Cy120/Ftu/TBI375 (N = 21, 60%) or chemotherapy-only (N = 14, 40%, 10 Clo/Mel/Thio, 4 Bu/Mel/Thio). GVHD prophylaxis was CNI/MMF. Units had a high degree of donor-recipient HLA-allele disparity (Table). The cumulative incidence of sustained donor neutrophil engraftment was 94% (95%CI:78-98, median 21 days, range 12-33), and hematopoiesis was mediated by a single unit. Day +180 platelet engraftment ≥ 50 x 10⁹/L was 82% (95%CI:64-92, median 51 days, range 39-299), CD4+ count recovery was prompt: mean day 60 201 (SD:+/-180), and day 120 250 (SD:+/-150). Of 33 engrafted pts, 10 (30%) engrafted with a unit with pre-cryopreservation TNC < 2.5 x 10⁷/kg, and 17 (51%) engrafted with a unit < 5/8 HLA-allele matched. The cumulative incidence of day 100 grade II-IV acute GVHD was 46% (95%CI:29-61), and 23% (95%CI:11-38) had grade III-IV acute GVHD. 3-year chronic GVHD was 14% (95%CI:5-28). With a median 58 month (range 20-105) follow-up, the 3-year cumulative incidence of TRM was 11% (95%CI:4-24); deaths were due to graft failure (2), HHV-6 encephalitis (1), and viral pneumonia (1). Relapse at 3 years was 20% (95%CI:9-35): 2 AML CR1 (one FLT-3 ITD, one M7), one previously refractory AML, and 4 ALL (2 CR1, 1 CR2, 1 CR3). None of the 4 pts transplanted with MRD+ relapsed. Three-year DFS was 68% (95%CI:50-81), with no difference based on diagnosis (p = 0.25, Figure), TBI-based cytoreduction (p = 0.68), or non-European ancestry (p = 0.24).

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**Figure:** 3-yr DFS after DCBT in children with high-risk acute leukemia.