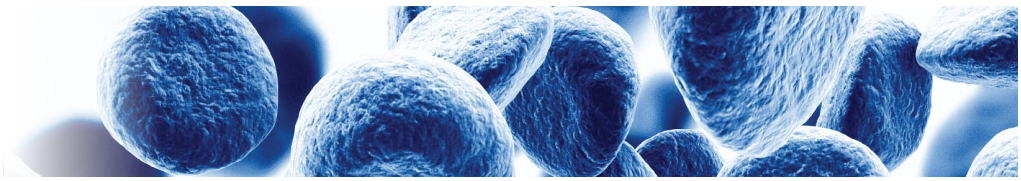

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Post-transplant administration of donor lymphocytes depleted of alloreactive T-cells (ATIR101) improves overall survival and reduces transplant related mortality following T-cell depleted haploidentical HSCT: Results from a Phase 2 Trial in patients with AML and ALL

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Background: Haploidentical donor grafts may resolve the shortage of available HLA-matched donors for hematopoietic stem cell transplantation (HSCT). However, to prevent graft-versus-host disease (GVHD), haploidentical HSCT requires alloreactive T-cell depletion. We have developed a strategy that allows additional donor lymphocytes to be infused post-HSCT without the risk of inducing severe GVHD and maintaining the ability to react against infections and leukemic cells.

Methods: In this open-label, multicenter phase 2 study (CR-AIR-007; NCT01794299), 23 patients with median age of 41 years (range 21 - 64) were treated with ATIR101. Seventeen patients had AML (74%), 12 in CR1 and 5 in CR2, and six patients had ALL (26%), 4 in CR1 and 2 in CR2 at the time of HSCT. Patients underwent myeloablative conditioning, consisting of a] TBI (1200 cGy; n=11) or b] melphalan (120 mg/m2; n=12), along with thiotepa (10 mg/kg), fludarabine (30 mg/m^2 x 5d) and ATG (2.5mg/kg x 4d). A CD34+ selected stem cell graft from a haploidentical donor was given, containing 10.9x10^6 CD34+ cells/kg (range;3.2 – 24.4). Donor lymphocytes were processed using a selective photodepletion technology, creating a donor lymphocyte infusion depleted of alloreactive T-cells (ATIR101). ATIR101 was infused at a median of 28 days post-HSCT (range; 28-73 days) at a fixed dose of 2x10^6 CD3+ cells/kg. No post-transplant GVHD prophylaxis was administered.

Results: All patients engrafted rapidly after transplantation, with neutrophil and platelet engraftment achieved at a median of 12 days (range 8-34, range 9-35 respectively). Mean follow-up at present is 292 days post-HSCT (as of November 23rd, 2015). A total of 19 patients were beyond 6 months post-HSCT, of which 15 were still alive at that time, and 15 patients were already 12 months post-HSCT, of which 10 were still alive. None of the patients developed grade III/IV acute GVHD after infusion of ATIR101. Two cases of grade II acute GVHD were reported thus far with a delayed onset, starting only at day 173 and day 247 post-HSCT. When compared to a matched historic control group (N=35), TRM was significantly lower in patients given ATIR101 after a T-cell depleted haplotransplant with a 6-month TRM for HSCT + ATIR101 of 15% versus 37% for HSCT only (Figure 1). Thus far two patients experienced a relapse within the first year, occurring at 61 and 90 days post-HSCT. One patient died as a result of the disease relapse. The overall survival of patients given ATIR101 was significantly improved compared to a historic control group, with a 1-year survival of 75% in the HSCT+ATIR101 group and 20% in the control group (Figure 2).

Conclusion: Administration of a high dose of donor lymphocytes in ATIR101 from a haploidentical donor does not cause severe GVHD without the use of prophylactic immune suppression. Addition of ATIR101 to a T-cell depleted HSCT protocol significantly improves transplantation outcome, with reduced TRM and improved OS. Moreover, the low number of relapses observed thus far is most encouraging and supports the hypothesis of preservation of T-cells in ATIR101 that are able to recognize leukemic antigens.

Figure 1: