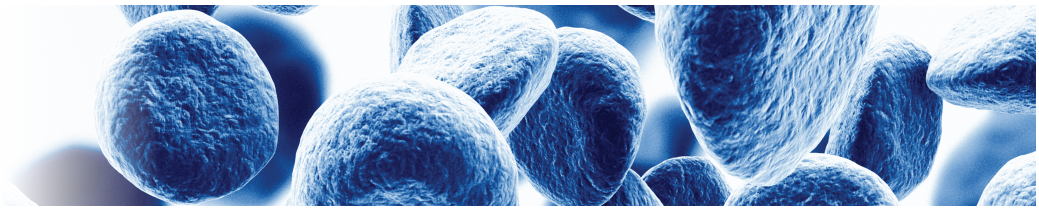

Abstract EBMT Meeting 2016

Donor lymphocytes depleted of alloreactive T-cells (ATIR101) improve overall survival and reduce transplant related mortality in a T-cell depleted haploidentical HSCT: Results from a Phase 2 Trial in patients with AML and ALL

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Introduction: Haploidentical donors may resolve shortage of available HLA-matched donors for treatment of blood cancer with a hematopoietic stem cell transplantation (HSCT). However, to prevent graft-versus-host disease (GVHD), haploidentical HSCT requires alloreactive T-cell depletion. We developed a strategy that allows additional donor lymphocytes to be infused post-HSCT without risk of inducing severe GVHD and maintaining reactivity against viruses and leukemic cells.

Material (or patients) and 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. Sixteen patients had AML (70%), 11 in CR1 and 5 in CR2, and seven patients had ALL (30%), 4 in CR1 and 3 in CR2/3 at time of HSCT. Patients underwent myeloablative conditioning, consisting of a] TBI (1200 cGy; n=11) or b] melphalan (120mg/m^2; 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 11x10^6 CD34+ cells/kg (range; 4.7–24.4) and 0.29x10^4 CD3+ cells/kg (range; 0–1.8). In addition, donor lymphocytes from the same donor 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 (range; 28-73) post-HSCT at a fixed dose of 2x10^6 CD3+ cells/kg, without use of post-transplant GVHD prophylaxis.

Results: All patients engrafted rapidly after transplantation, with neutrophil and platelet engraftment achieved at a median of 12 days (range 8-34 and 9-35 respectively). Median follow-up (as of November 23rd, 2015) is 292 days post-HSCT. A total of 19 patients were beyond 6 months post-HSCT, of which 15 were alive at that time, and 15 patients were already 12 months

post-HSCT, of which 10 were alive. No patients developed grade III/IV acute GVHD after infusion of ATIR101. Two cases of grade II acute GVHD were reported with a delayed onset, starting only at day 173 and day 247 post-HSCT. No patient died within 100 days post-HSCT and there were 3 deaths as a result of TRM (all infections) within 6 months post-HSCT. When compared to a historic control group (N=35), TRM was significantly lower in patients given ATIR101 after a T-cell depleted HSCT with a 6-month TRM for HSCT + ATIR101 of 15% versus 37% for HSCT only (Figure 1a). Thus far two patients experienced a relapse within the first year, occurring at 60 and 90 days, respectively, 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 1b).

Conclusion: Administration of a high dose of donor lymphocytes in ATIR101 from a haploidentical donor does not cause severe GVHD without 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 able to recognize leukemic antigens.

Figure 1: