Abstract: S274

Title: A NEW, EFFECTIVE, SAFE, NON-MYELOABLATIVE CONDITIONING REGIMEN WITH A HLA-MATCHED SIBLING DONOR FOR THE SEVERE SICKLE CELL PHENOTYPE IN ADULTS

Abstract Type: Oral Presentation

Session Title: Novel therapies in hemoglobinopathies

Background:

Sickle cell disease (SCD) is an inherited disorder that affects over 5 million people worldwide. Allogeneic hematopoietic stem cell transplantation (HSCT) from a matched related donor is the only curative treatment for SCD. Alternative conditioning regimens for hematopoietic stem cell transplantation with a matched sibling donor (MSD) have shown good results for adults with SCD. The National Institutes of Health (NIH) developed a new nonmyeloablative (NMA) conditioning regimen (low-dose total body irradiation (TBI) and alemtuzumab). They reported promising results in adults with SCD but rate of graft rejection remained around 13%.

Aims:

In view of these results, we decided to perform HSCT for adult patients with severe SCD when a matched, related donor was available. Since the French health authorities had not authorized alemtuzumab for this indication at that time (2015), we designed a NMA conditioning regimen with fludarabine, cyclophosphamide, low-dose TBI, and rabbit antithymocyte globulin (ATG).

Methods:

Three months before the conditioning, the enrolled patients were placed on a regular transfusion program based on erythrocytapheresis; the objective was to maintain the hemoglobin S (HbS) level below 30%, suppress erythropoiesis, and stabilize SCD. The conditioning regimen consisted of fludarabine 30 mg/m^2 per day from day -6 to day -2, cyclophosphamide 50 mg/kg per day on day -6, and rATG 0.5 mg/kg on day -6 and then 2.5 mg/kg per day from day -5 to day -2. A single TBI session (dose: 200 mGy) was performed on day -1. The stem cells were sourced from bone marrow from a matched sibling donor. Prophylaxis for GvHD consisted of rapamycin and mycophenolate mofetil.

Results:

Seven adults SCD patients with a median age of 27.1 years have been treated. The conditioning was well tolerated and toxicity profile was very acceptable. Rapamycin was well tolerated except a case of nephrotic syndrome related to pre-existing SCD nephropathy and one case of PRES arose two years after HSCT in a context of untreated, chronic hypertension and potential vascular sequelae of SCD. No graft failure was observed. None of the patients had acute grade II-IV GvHD or extensive chronic GvHD almost 2 years after HSCT except patient n°1 who was inobservant. All patients had full donor chimerism, over 70%, in the year after HSCT and full donor erythroid chimerism regarding the level of HbS after HSCT, which was the same as in their donors (figure 1). The hemolytic parameters and hemoglobin level normalized in the first year post-HSCT with no recurrence of vaso occlusive events.

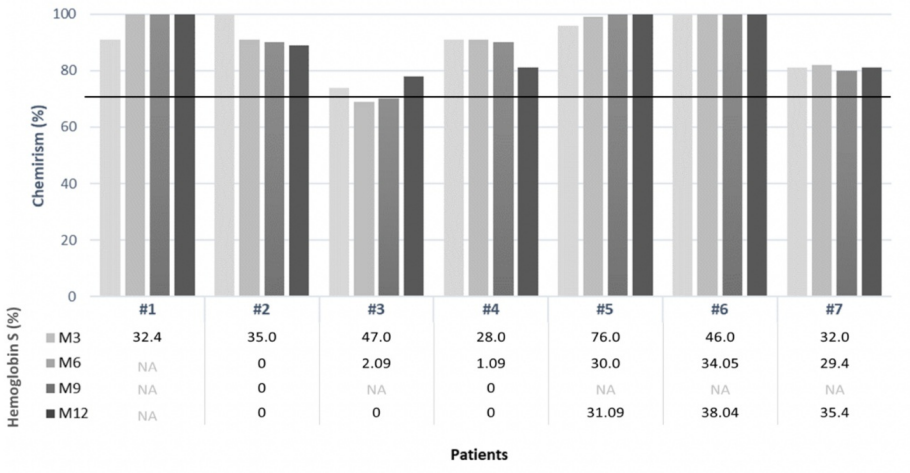
Summary/Conclusion:

Although the number of patients was small, the first results are very encouraging. The tolerance was excellent with low toxicity. Only few infections occurred after HSCT and controlled with adequate medication.

Compared to the NIH protocol (TBI 300 mGy and Alemtuzumab), all patients had a full donor myeloid chimerism, over 70%, in the year after HCT without serious GVHD (except patient n°1 who did not take his medication). Furthermore, all patients had full donor erythroid chimerism regarding the level of HbS after HSCT, which was the

same as in their donors. We hypothesized that a better control of erythropoiesis with optimal transfusion program before HSCT and the use of rATG contributes to a better engraftment. Moreover, Eapen et al. have reported cases of acute myeloid leukemia and myelodysplastic syndrome after graft rejection in patients transplanted for SCD. Despite mixed chimerism is sufficient to reverse SCD phenotype, a full donor chimerism is likely to be the best way to avoid graft rejection and clonal expansion of leukemic cells. For these reasons, our condition might be a good choice regarding the level of chimerism without severe GvHD.

Figure 1. Evolution of chimerism and level of HbS in the year after Hematopoietic Stem Cell Transplantation (HSCT) for each patient



	#1	#2	#3	#4	#5	#6	#7
M3	32.4	35.0	47.0	28.0	76.0	46.0	32.0
M6	NA	0	2.09	1.09	30.0	34.05	29.4
M9	NA	0	NA	0	NA	NA	NA
M12	NA	0	0	0	31.09	38.04	35.4

Keywords: Allogeneic bone marrow transplant, Sickle cell anemia, Sickle cell disease