Allogeneic Hematopoietic Stem Cell Transplantation (allo HSCT) in Patients with IPSS Low or Intermediate-1 Myelodysplastic Syndrome (MDS): A Prospective Multicenter Phase II Study Based on Donor Availability By the GFM & SFGM-TC "MDS-ALLO-Risk"

Authors: Marie Sebert, Cendrine Chaffaut, Sylvain Thepot, Corentin Orvain, Thomas Cluzeau, Michael Loschi, Pierre Peterlin, Patrice Chevallier, Maud d'Aveni, Marie-Thérèse Rubio, Odile Beyne Rauzy, Anne Huynh, Amandine Charbonnier, Nathalie Fegueux, Gaelle Fossard, Stephanie N'guyen-Quoc, Sophie Park, Rosa Sapena, Fatiha Chermat, Lionel Ades, Sylvie Chevret, Pierre Fenaux, Marie Robin

Background:
Allo HSCT is a potentially curative treatment in MDS which, in higher risk (IPSS high and int 2) MDS demonstrated an overall survival (OS) advantage over conventional treatment (especially HMAs) in retrospective (Koreth et al., JCO 2013) and prospective (Robin et al. leukemia 2015) studies. Retrospective studies, on the other hand, suggested no OS advantage for allo HSCT in lower risk MDS (IPSS low and int 1), except possibly in the "poorest" lower risk MDS subsets, as classified by the WPSS (Alessandrino et al. AMJH 2013) However, about 25% of lower risk MDS patients are reclassified as higher risk by the R-IPSS and a proportion of other lower risk MDS can also harbor some higher risk features that compromise their outcome. MDS-ALLO-RISK trial (clinicaltrial.gov NCT02757989), was designed to assess outcome of lower risk MDS patients with some high-risk features after HLA-matched donor HSCT.

Method:
The primary objective of this study was to demonstrate an OS improvement in lower risk MDS patients with some high risk features with a donor compared with those without a donor (with a 3 year OS of 70% versus 40%, respectively) . Inclusion criteria were: IPSS low or int1 MDS with at least one of the following characteristics: 1) R-IPSS intermediate or higher 2) RBC transfusion dependent anemia and failure to two or more treatments (including EPO, Lenalidomide or HMA); 3) platelets < 20 G/L requiring transfusions 4) ANC < 0.5 G/L with severe infection 5) no contra indication to allo HSCT 6) age <70 years 7) HLA identical donor (sibling or 10/10 unrelated) 105 inclusions were planned: 62 in group with a donor (group A) and 43 in group without a donor (group B). Recruitment began in June 2016 and stopped in March 2021 due to futility on the interim analysis. Median follow-up was 20 months. Data cut off analysis was June 2021.

Results:
79 patients were included, 64 in group A and 15 in group B. Median age was 62.4 (IQR: 58-65) years in group A and 66 (IQR: 60.5-68) years in group B. Patients in group A were more frequently males (73 vs 40%, p=0.029), WHO was CMML in 8 (10%), MDS-SLD in 5 (8%), MDS-MLD in 9 (11%), MDS-EB1 in 41 (52%), MDS-RS in 12 (15%), unclassified in 4 (6%) without significant differences between the two groups. IPSS /IPSS-R was similar in both groups: IPSS low in 10% (11% in group A and 7% in group B) and Int-1 in 90%. IPSS-R: very low risk (6% vs 0%); low risk (25% vs 27%); intermediate (50% vs 47%); high (19% vs 27%); no very high risk. Among the 64 patients with a donor, 58 (92%) received HSCT, 2 died before HSCT; 2 had progressive disease and 2 are planned for HSCT. Transplanted patients received reduced intensity conditioning regimen with busulfan 6.4mg/kg, fludarabine 150mg/m2 and ATG (rabbit antithymocyte globulin therapy, grafalon®) 30mg/kg and cyclosporine-mycophenolate

mofetil as GVHD prophylaxis. In group A, 21/64 had died, including 13 died from a non-relapse cause. In group B, 4/15 patients had died, 3 from MDS progression and one from CNS bleeding. Three-year OS was 60% (95%CI: 46.9-76.8) in group A and 64.2% (41.3-99.6) in group B (p=NS). At the time of analysis, 20 and 5 patients had progressed/relapsed in group A and B respectively. with a cumulative incidence of relapse/progression (from inclusion) of 27.4% (IC95%: 15;39.8) in group A and 41.7% (IC95%:9.2;74.2) in group B (p=0.71). Among the 58 transplanted patients, 11 (19%) died without disease progression, including one death from a solid tumor. 3 years non-relapse mortality in transplanted patients was 23.4% (IC95%:9.7;37). 3 years Incidence of grade 2 to 4 acute GVHD was 40.8% and 3 years chronic GVHD was 24.9%.

Conclusions:

In this, to our knowledge, first prospective study in IPSS lower risk patients with some unfavorable clinical or biological features, HLA identical donor (sibling or 10/10 unrelated) HSCT yielded a 3-year OS of 60%. Non relapse mortality was however 23%, and OS somewhat lower than expected (70% at 3 years) and similar to that observed in patients without a donor. Long-term follow-up is needed to better define subgroups of IPSS lower risk MDS that may benefit from allo HSCT.